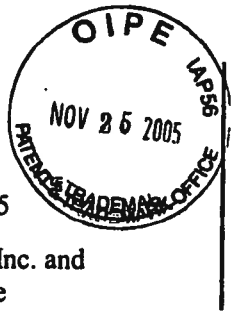
EXHIBIT 14

Reexam

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



Control No.:	90/007,542	Group Art Unit:	3991
Confirmation No.:	7585	Examiner:	B. Celsa
Filed:	13 May 2005		
Patent Owner:	Genentech, Inc. and City of Hope		
For:	Reexamination of U.S. Patent No. 6,331,415		

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COMMISSIONER FOR PATENTS
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RESPONSE UNDER 37 C.F.R. § 1.550(b)

Sir:

This communication is responsive to the Patent Office's communication mailed September 13, 2005. Owners note that on October 26, 2005, they filed a petition for extension of time to respond to the Patent Office's September 13, 2005 communication. That petition was granted by James Dwyer, the Director for the Central Reexamination Unit, on November 7, 2005, extending Owner's time to respond to the Patent Office's communication through November 27, 2005. The owners of U.S. Patent No. 6,331,415 respectfully request reconsideration of the rejection of the claims in view of the following remarks.

Remarks begin on Page 4.

Table of Contents

I. Overview of the Response

In the September 13, 2005 Office Action, the Office rejected the independent claims and certain dependent claims of U.S. Patent No. 6,331,415 (the '415 patent) for obviousness-type double patenting solely in view of certain claims of U.S. Patent No. 4,816,567 (the '567 patent). The Office also has rejected the remaining dependent claims of the '415 patent for obviousness-type double patenting based on certain claims of the '567 patent taken in view of several printed publications and patents.

The '415 patent claims are directed to production of immunoglobulin molecules or immunologically functional fragments comprising at least the variable domains of the heavy and light immunoglobulin chains. These claims require the production of both heavy and light immunoglobulin chains in a single host cell. The '567 patent claims, by contrast, do not require production of an immunoglobulin molecule or an immunologically functional fragment. They also do not require that both the heavy and the light chains be produced in one host cell. Instead, they recite, and thus require only that a single chimeric immunoglobulin light or heavy chain be produced, and that the end result of the process be a heavy or light chimeric immunoglobulin chain polypeptide.

Each of the rejections is premised on an incorrect characterization of the claims of the two patents, and on numerous factual and legal errors. In summary:

- The Examiner improperly construes the claims of the '415 and '567 patents. Specifically, the Examiner incorrectly portrays claims of the '567 patent as defining "species" included within the scope of what he believes are "genus" claims in the '415 patent, which, under his logic, would cause the '567 patent claims to anticipate the '415 patent claims. The Examiner's errs by comparing only one feature shared by the claims of the two patents (i.e., whether the immunoglobulin chains are "chimeric" or not), instead of comparing what each claim, considered as a whole, defines. When the claims are construed properly, it is apparent that the inventions claimed in the '567 patent and the inventions claimed in the '415 patent are not related as species and genus.
- The Examiner improperly focuses on the fact that claims of the '567 patent "read on" and thus "dominate" subject matter also claimed by the '415 patent. This is legally irrelevant to the question of obviousness-type double patenting. Instead, an obviousness-type double patenting analysis must compare what the claims of the second patent require relative to what claims of the first patent require. The claims of the '567 patent and the claims of the '415 patent recite, and therefore require, different elements or features.

- Each of the rejections of the remaining dependent claims of the '415 patent is grounded on the Office's incorrect finding that the underlying independent claim is anticipated by the '567 patent. The Examiner engages in an overly simplistic exercise of locating in the prior art references the elements required by the '415 dependent claims that are missing from the '567 patent claims. The Examiner's approach mischaracterizes the teachings and suggestions of the cited references, and what those references would have suggested to a person of skill in the art in early April of 1983. Read properly, none of the cited references would have rendered the dependent claims of the '415 patent obvious to a person of skill in the art in early April of 1983.

- The rejections of all of the '415 patent claims for obviousness-type double patenting contradict numerous past findings by the Board of Patent Appeals and Interferences (the "Board") and different Examiners that claims to production of immunoglobulin molecules or immunologically functional fragments requiring production of heavy and light chains in a single host cell are separately patentable from claims that do not require production of both heavy and light chains in a single host cell.

The rejections of the claims of the '415 patent thus are plainly improper and should be withdrawn.

During the interview on October 25, 2005, the Examiners invited Owners to provide their views on two prior art references, namely, U.S. Patent No. 4,399, 216 to Axel et al ("Axel") and Rice et al., Proc. Natl. Acad. Sci. USA 79:7862-7865, December 1982 ("Rice").

Owners note that the Office has not rejected the independent claims of the '415 patent based on the '567 patent claims, taken in view of Axel, Rice, or any other prior art. Similarly, neither the Third Party Requestor nor the Office in its Order for Reexamination has suggested that the claims of the '567 patent, taken in view of Axel, Rice, or any other prior art, would have rendered the independent claims of the '415 patent obvious. Rejecting the independent claims of the '415 patent as being obvious from the '567 patent claims taken in view of Axel or Rice would contradict repeated findings by the Office that the independent claims of the '415 patent are not obvious over the '567 claims. Doing so would present an entirely new ground of rejection not suggested in the Office Action of September 13, 2005, the Order establishing this reexamination, or even the Third Party Request.

Nonetheless, Owners provide comments on Axel and Rice in response to the Examiner's invitation at the interview to do so. As explained below, neither Axel nor Rice would have suggested to a person of skill in the art, in early April of 1983, that the inventions defined by the '415 patent claims are obvious variants of the '567 claims. Simply put, neither

Axel nor Rice suggests producing immunoglobulin molecules or immunologically functional fragments by producing heavy and light immunoglobulin chains in a single transformed host cell.

II. Information Disclosure Statement

An information disclosure statement will be filed shortly after this response. The Examiner is respectfully requested to acknowledge receipt and review of the items provided with the information disclosure statement.

III. Interview Summary

On October 25, 2005, Representatives of the Owners ("Representatives") participated in an interview with Examiners Celsa, Vollano, Huang, Helms and Blanchard. The interview was requested to discuss the basis of the rejections set forth in the Office Action dated September 13, 2005. In addition, per the request of Examiner Blanchard, the interview addressed questions regarding the distinctions between the processes defined by the claims of the '415 patent and those defined by the claims of the '567 patent.

During the course of the interview, the Examiners indicated that the primary basis of the rejections set forth in the Office Action was their view that the claims of the '415 patent defined a "genus" that encompassed "species" claimed in the '567 patent. The Examiners also indicated that the other references cited in the Office Action were being relied upon primarily to address features of the rejected dependent claims of the '415 patent that were not found in the claims of the '567 patent.

Representatives provided an overview of the distinctions between the claims of the '415 patent and the claims of the '567 patent and explained that they are not related as genus and species, respectively. Representatives also addressed the law governing double patenting.

During the interview, the Examiners invited Owners to address certain issues in Owner's response to the Office Action, and information regarding events that occurred during the prosecution of the application that matured into the '415 patent (i.e., U.S.S.N. 07/205,419, or the '419 application). These included:

(i) a brief summary of the prosecution of the '419 application, including the claim amendments made, and the substance of the interview conducted on October 4, 2001;

(ii) an explanation of the restriction requirements imposed in the '419 application, including whether these restrictions were at any point withdrawn or mooted by claim amendments, and how the various claims presented during the prosecution of the '419 application related to the restriction requirements;

(iii) an overview of the interference proceeding that involved the '419 application, along with a copy of the judgment rendered in the resulting § 146 action;

(iv) an explanation of the meaning of "heavy or light chain having specificity for a particular known antigen" as that phrase is used in the claims of the '567 patent; and

(v) the relevance, if any, of Axel or Rice, to the question of obviousness of the processes defined in the '415 patent in view the '567 patent.

Information responsive to items (i) to (iii) is provided in section IV, below, and in the Declaration of Wendy M. Lee under 37 C.F.R. § 1.132 ("Lee Declaration"). Information responsive to items (iv) and (v) is provided in section V, below.

IV. Summary of Litigation Activity and Related Proceedings Concerning U.S. Patent No. 6,331,415 (the '415 patent).

A. MedImmune v. Genentech Proceeding

The '415 patent was at issue in a Declaratory Judgment action brought against Genentech, Inc., et al. by MedImmune, Inc. in the Central District of California (Case No. CV 03-2567). The lawsuit included claims for violation of antitrust and unfair competition laws and for patent invalidity. The District Court entered summary judgment in favor of Genentech, et al. on all the antitrust and unfair competition claims and dismissed the patent invalidity claims as being nonjusticiable under the Declaratory Judgment Act. See, MedImmune, Inc. v. Genentech, Inc., CV 03-2567 (C.D. Cal. Jan 14, 2004; February 18, 2004; April 26, 2004). The Court of Appeals for the Federal Circuit affirmed the decisions of the District Court. See, MedImmune, Inc. v. Genentech, Inc., No. 04-1300/04-1384 (Fed. Cir. October 18, 2005). MedImmune has filed a petition for a writ of certiorari to the United States Supreme Court in connection with this decision; a decision on that petition is now pending. Copies of the District Court and Federal Circuit opinions, and the MedImmune petition are provided for the convenience of the Office in Exhibit A to this response.

B. Celltech v. Genentech Interference Proceeding

The application that issued as the '415 patent (i.e., U.S.S.N. 07/204,419) was involved in Interference No. 102,572 (the '572 interference) with U.S. Patent No. 4,816,397, issued to Boss et al. (the "Boss" patent) on March 28, 1989. That same day, the PTO issued the '567 patent to Cabilly. A brief summary of this interference and its relevance to the present reexamination proceeding is provided below in response to the invitation of the Examiners at the October 25, 2005, interview. The Examiner is also invited to consider a simplified timeline of the prosecution of the '419 application, provided as Exhibit B to this response, as well as the Lee Declaration, provided herewith.

1. Prosecution of the '419 Application Prior to Interference

The '419 application was filed on June 10, 1988 as a Rule 60 continuation application of U.S.S.N. 06/483,467 that ultimately issued as the '567 patent. On March 6, 1990, the PTO imposed requirements for restriction and election of species in the '419 application (see paper no. 4; Lee Declaration, Exhibit B). The restriction was between processes, vectors and host cells on the one hand, and compositions of insoluble heavy chain, light chain or Fab fragments, on the other. In the election of species requirement, the Examiner found claims to vectors, transformed host cells and processes for making an immunoglobulin heavy or light chain to be patentably distinct from vectors, host cells and methods of making an "immunoglobulin heavy chain AND light chain.(capitals in original)"

On March 9, 1990, Owners amended the '419 application by canceling the then-pending claims of the '419 application (which were the subject of the March 6, 1990 restriction and election of species requirement) and by adding new claims corresponding to claims 1 to 18 of the Boss patent. See, '419 application, paper no. 5; Lee Declaration, Exhibits C and D. Owners observed in this amendment that while the method specified in the copied claims can be used for making chimeric immunoglobulins, it is not necessary to use that method when practicing the methods claimed in the '567 method "since the chimeric immunoglobulin chains can be produced in host cells transformed only with heavy or light chain, but not both" (emphasis in original) as called for in the copied Boss patent claims. Owners also expressed their view that the Office, by issuing the Cabilly '567 patent claims and the Boss patent claims as separate patents, had concluded that these two sets of claims defined separately patentable inventions.

On March 30, the Examiner issued a communication indicating that he viewed cancellation of the then-pending claims as non-responsive to the restriction requirement in that application. See, '419 application, paper number 6; Lee Declaration, Exhibit E. On May 2, 1990, owners re-introduced certain of the canceled claims and affirmatively elected the species concerning "vectors, hosts and methods of making an immunoglobulin heavy chain AND light chain (in insoluble form)." See, '419 application, paper 8; Lee Declaration, Exhibit F. To correct typographical errors in the numbering of the claims added to the '419 application, two subsequent amendments were made (See, Lee Declaration, particularly paragraph 9, and Exhibit C to this response, which provides a detailed summary of the claim amendments made in the '419 application).[1]

On September 7, 1990, the PTO imposed another restriction requirement. See, '419 application, paper no. 11; Lee Declaration, Exhibit I. In this restriction, the PTO differentiated claims 67 to 86 (which required independent expression of heavy and light immunoglobulin chains in a single host cell, and thus corresponded to the claims of the Boss patent) from claims 87 to 100 (which did not require the heavy and light chains to be produced in a single host cell). The Examiner provided the following justification:

> Inventions Group I and Group II are distinct and independent of each other, and as such, **will support separate patents**. The method of Group I is drawn to immunoglobulin chains which are independently expressed in the transformed host cell while the method of the second Group does not make this distinction. Further Group I refers to the antibody fragment composed of both heavy and light variable regions whereas Group II refers to a fragment composed of the either the heavy or light chains with variable and constant regions present in each chain (underlined emphasis in original, bold emphasis added).

The Examiner thus held claims corresponding to the '415 patent claims were patentably distinct from claims that did not require production of heavy and light immunoglobulin chains in a single host cell.

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[1] Claims 88-100 of the supplemental amendment filed on July 19, 1990, depended from cancelled claims 53, 58, 59, or 66, rather than from 87, 92, 93 or 99. The Examiner disregarded these typographical errors for purposes of the restriction requirement. The further supplemental amendment filed August 24, 1990

A third supplemental amendment was filed on September 13, 1990 ('419 application, paper 12) to respond to concerns raised by the Examiner as to formal matters. In that amendment, claims 67-100 were canceled and were reintroduced as (renumbered) claims 101-134. See, Lee Declaration, Exhibit K. Aside from the renumbering of the claims, claims 101-120 were the same as claims 67-86 (Group I claims) and claims 121-134 were the same as claims 87-100 (Group II claims). See, Exhibit C to this response. Thus, following this third supplemental amendment, claims 101-135 were pending in the '419 application. Claims 101-120 corresponded to claims 1-18 of the Boss patent. Claims 121-134, however, were directed to inventions that did not require the production of both the heavy and the light immunoglobulin chain in a single host cell.

2. Summary of the '572 Interference

On February 28, 1991, the Board of Patent Appeals and Interferences (BPAI) declared an interference (the '572 interference) between the copied claims (claims 101-120) in the '419 application and claims 1-18 of the Boss patent. See, '419 application, paper no. 11; Lee Declaration, Exhibit L. The count was defined to be claim 1 of the Boss patent, which was identical to claim 101 of the '419 application. As such, the count defined a process in which a single host cell is transformed to independently express DNA sequences encoding heavy and light immunoglobulin chains, and further requires that an immunoglobulin molecule or immunologically functional immunoglobulin fragment result from the process.

When the Board declared the interference, it excluded claims then pending in the '419 application that did not require a single host cell to be transformed with DNA sequence encoding both a heavy and a light immunoglobulin chain. See, Lee Declaration, Exhibit L. Specifically, claims 101 to 120 (corresponding to claims 1-18 of Boss) were designated as corresponding to the count, while claims 121 to 134 were designated as not corresponding to the count. These undesignated claims were never added to the interference. The Board confirmed this in its "Final Order After District Court Judgment", ('419 application, paper no. 18 and Lee Declaration, Exhibit N). See, particularly paragraphs C.4 to C.6. The Board thus twice confirmed that claims that did not require production of heavy and light chains in one host cell did not correspond to the count of the interference, which did require production of heavy and light chains in one host cell.

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correcting informal errors in claim dependency for claims 88-100 was entered after issuance of the

A determination by the Board that claims do not correspond to the interference count reflects the Board's determination that such claims are separately patentable over the count. As explained in In re Van Guens, 988 F.2d 1181, 1185 (Fed. Cir. 1993):

> "When an interference is declared between a patent and an application, the PTO rules require that "[a]ll claims in the application and patent which define the same patentable invention as a count shall be designated to correspond to the count." 37 C.F.R. §1.606. The PTO rules define what is meant by the same patentable invention with the following example:
>
> Invention A is the "same patentable invention" as an invention "B" when invention "A" is the same as (35 U.S.C. 102) or is obvious (35 U.S.C. 103) in view of invention "B" assuming invention "B" is prior art with respect to invention "A". 37 C.F.R. § 1.601(n) (emphasis added)."

Thus, by not designating claims 121 to 134 of the '419 application as corresponding to the count, the Board found that the claims that eventually issued in the '415 patent were separately patentable in view of claims which did not require the production, in a single host cell, of both heavy and light immunoglobulin chains, and vice versa.[2]

Like claims 121 to 134 of the '419 application, the claims of the '567 patent were never designated as corresponding to the count of the '572 interference. In fact, during the interference, the Board was presented with the question of whether to add the '567 patent to the '572 interference, and declined to do so. Specifically, on June 5, 1991, Cabilly requested the Examiner-in-Chief (EIC) to exercise her discretion to add a then-pending Boss application. The claims in that application were rejected and had been restricted from the claims in the Boss patent involved in the interference. Boss responded to this request by asserting that the claims in the application had not been allowed, but added that if the EIC exercised her discretion to add this Boss application, that she should also add the '567 patent to the proceeding. In a July 26, 1991 decision, the Board declined to add either the Boss

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restriction requirement.

[2] See, MPEP 804, subsection II.B.1, which observes that "[s]ince the analysis employed in an obviousness-type double patenting determination parallels the guidelines for a 35 U.S.C. 103(a) rejection, the factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are employed when making an obvious-type double patenting analysis."

application or the Cabilly '567 patent to the proceeding. See, Lee Declaration, particularly Exhibit M.

As noted above, the decision of the Board to not add the '567 patent to the interference is an additional consistent finding by the Board that the claims of the '567 patent did not anticipate or render obvious claim 1 of the '415 patent. This is the only logical explanation for the Board's decision to not add the '567 patent claims to the '572 interference. When the Board decides to not designate claims as corresponding to a count, that decision represents a determination by the Board that the count is separately patentable over those claims, and vice versa, because the claims and the count do not define the "same invention" (i.e., a claimed invention that is anticipated or rendered obvious by the other claimed invention).

On August 13, 1998, the Board issued a final judgment awarding priority to Boss. On October 9, 1998, pursuant to 35 U.S.C. § 146, Owners filed a civil action in the Northern District of California (Case No. C98-3926 MMC).[3] Subsequently, Genentech and Celltech, Ltd., the assignee of the Boss patent, entered into an agreement which provided a basis for settling the litigation. On March 16, 2001, the district court entered judgment on the issue of priority in favor of Genentech. A copy of the judgment entered in the § 146 action in the Northern District of California is provided for the convenience of the Office as Exhibit D to this response.

As a consequence of the Court's disposition of the § 146 action, on July 25, 2001, the Board vacated its August 13, 1998 decision, awarded priority to Cabilly, and returned the '415 application to the Examiner to take action as deemed "appropriate with respect to Cabilly claims 121-134 which were not involved in the interference." See, '419 application, paper no. 18; Lee Declaration, Exhibit N, at page 14.

3. Prosecution of the '419 Application Subsequent to Termination of Interference

On October 4, 2001, Owners participated in an interview with Examiners

[3] During the § 146 action, Owners were able to present stronger evidence of conception prior to Celltech's March 25, 1983 priority date than they had been able to present in the interference proceeding. Under then-existing law, Celltech – a U.K. company – could not establish priority based upon inventive activities that occurred outside the United States. Celltech was limited to a conception date no earlier than its U.K. priority filing date of March 25, 1983. See 35 U.S.C. §§ 104, 119 and 365.

Gambel and Hutzell in which obviousness-type double patenting issues relative to the claims of the '567 patent were discussed. See, Lee Declaration, paragraphs 20 to 23. In that interview, the Examiner found that claims requiring expression of heavy and light immunoglobulin chains in a single host cell did not raise any obviousness-type double patenting issues relative to the claims of the '567 patent. The Examiner also discussed the relationship of the then-pending claims, including claims 121 to 134, which were not involved in the interference, to the restriction of record.

In response to these discussions, Owners amended claims 121 to 134 in an amendment filed the day of the interview that limited them to embodiments which required both heavy and light immunoglobulin chains (or Fab fragments thereof) to be produced in a single host cell. See, e.g., '419 application, paper no. 24; Lee Declaration, Exhibit P. The amendments were motivated by the Owner's understanding from the interview that such amendments were necessary to ensure that these undesignated claims fell within the Group I invention of the restriction imposed on September 7, 1990, which Owners also understood remained in effect. See, Lee Declaration, paragraph 23. These claims (claims 101 to 120, amended claims 121-134, and new claims 135-138[4]) subsequently issued in the '415 patent on December 18, 2001.

C. Past Findings of the PTO During Prosecution of the '415, '567 and Boss Patents Establish that the Claims of the '415 Patent Are Patentably Distinct from the Claims of the '567 Patent

As the foregoing establishes, the Office, on numerous occasions, specifically addressed the question of whether claims that required production of heavy and light immunoglobulin chains in a single host cell are separately patentable over claims that do not. Each time the Office addressed this question, it consistently found that the two sets of claims were separately patentable. And the Office made these findings despite the fact that these claims "read on" situations where both heavy and light chains are produced in a single host cell.

[4] New claims 135 to 138 issued as claims 33 to 36 of the '415 patent. Claim 135 was a new independent claim, while claims 136 to 138 were new dependent claims. Claims 136 and 137 were ultimately dependent on claim 101, while claim 138 was dependent on new claim 135. Claim 135 is directed to a process where heavy and light chains are expressed in a single host cell. The new independent and dependent claims all fall within the enumerated boundaries of Group I of the restriction requirement imposed on September 7, 1990.

Moreover, these consistent findings were made not only by different Examiners, but by the Board. Specifically:

- In the '572 interference, the Board did not designate claims 121 to 134 of the '419 application as corresponding to the count. Those claims read on production of heavy or light chains in a single host cell, but only require production of a single chimeric heavy or light immunoglobulin chain in a single host cell. The Board also elected not to involve the '567 patent in the interference. The '567 patent claims, like claims 121 to 134 of the '419 application, do not require expression of both heavy and light chains in a single host cell. These actions reflect the conclusions of the Board that the claims of the '567 patent do not anticipate or render obvious the claims of the '415 patent, and vice versa.

- During the interview of October 4, 2001, the Examiners indicated that no obviousness-type double patenting issues existed for claims requiring production of heavy and light chains in a single host cell relative to the claims of the '567 patent. In response to this observation, the undesignated claims were amended, limiting them to embodiments requiring the production of heavy and light chains in a single host cell.

- Restrictions were imposed by two different Examiners during the prosecution of the '415 patent that held that claims requiring production of both heavy and light immunoglobulin chains in a single host cell were patentably distinct from claims that read on – but did not require – producing both chains in a single host cell. These restrictions reflect the Examiners' determinations that these two sets of claims define independent and distinct inventions, and can support separate patents.

- The PTO examined the application that led to the Boss patent (requiring production of heavy and light chains in one host cell) at the same time as the application that led to the '567 patent, and the two patents were issued on the same day. Yet, the Office never declared an interference between these Boss and Cabilly applications, and it did not involve the Cabilly '567 patent in the interference between the Boss patent and the application that issued as the '415 patent.

Owners and the public have relied upon these repeated findings by the Office that the claims of the '415 patent are patentably distinct from the claims of the '567 patent. For the Office to discard these past findings, and reach the exact opposite conclusion, would be manifestly improper and unfair, particularly at this point in time long after the patents have issued. Owners submit that the '415 patent claims, consistent with the PTO's past determinations, are

not unpatentable for obviousness-type double patenting over the claims of the '567 patent, whether considered alone or in conjunction with the prior art.[5]

V. Response to Rejections

A. Basis of the Rejections as Set forth in the Office Action

Claims 1 to 36 of the '415 patent have been rejected under the judicially created doctrine of obviousness-type double patenting in view of claims 1 to 7 of the '567 patent, and, as to certain claims, further in view of Axel (U.S. Patent No. 4,399,216), Rice (Proc. Natl. Acad. Sci. USA 79:7862-7865, December 1982), Kaplan (EP 0 044 722), Accolla (Proc. Natl. Acad. Sci. USA 77(1):563-566, January 1980), and Builder (U.S. Patent No. 4,511,502).

Each of the rejections as set forth in the Office Action is ultimately based on the Examiner's view that claims 1, 13, 15-18, 21 and 33 each define a genus that includes within its scope a corresponding species defined by claims 1, 2, 5, 6 and 7 of the '567 patent. For example, at page 7 of the Office Action, under the heading, "The '567 patent claims a species of the genus claimed in the later '415", the Examiner states:

> "claims 1, 21 and 33 [of the '415 patent] are drawn [to] methods for producing a genus of immunoglobulins and claim 1 of the '567 [patent] is directed to methods for producing "chimeric" immunoglobulin chains, which is a species of the immunoglobulin genus claimed in the later '415 patent."

Similarly, on pages 7 and 8, the Examiner suggests that claims 13 and 15-18 of the '415 patent define "genus" inventions including corresponding "species" defined in claims 2, 5, 6 and 7 of the '567 patent. Specifically, the Examiner states:

> The same applies for the vector (claim 5) and host cell (claim 7) claims of the '567 patent and the corresponding claims 15-16 (vector) and 17-18 (host cell) of the '415 patent. Further claim 1 of the '567 patent recites a chimeric immunoglobulin species of the sub-genus defined by claim 13 of the '415 patent and claims 2 and 6 of the '567 patent are directed to a

[5] Owners also acknowledge the Examiner's finding that no issue of double patenting based on In re Schneller, 397 F.2d 350 (CCPA 1968) exists for the '415 patent in view of the '567 patent.

human constant region of the chimeric immunoglobulin, which is another example of a species within the genus claimed in the '415 patent.

The Examiner explains why he believes these claims are related as "genus and species" at page 8 of the Office Action:

> Applicant is reminded that the term 'comprising' recited in claim 1 of the earlier '567 patent is inclusive or open-ended and does not exclude additional, unrecited elements or method steps (MPEP 2111.03). Thus, while the claims of the '567 patent embrace embodiments in which separate host cell cultures express either a chimeric heavy or light immunoglobulin chain, the claims also read on embodiments in which one host cell culture expresses both heavy and light chains, at least one of which is chimeric.[6] Thus, claims 1-2 and 5-7 of the '567 patent read upon claims 1, 13, 15-18, 21 and 33 in the later '415 patent.

Claims in the '415 patent other than claims 1, 13, 15-18, 21 and 33 are not rejected exclusively on the basis of claims 1, 2, 5, 6 and 7 of the '567 patent. Instead, as the Examiner states at page 5 of the Office Action:

> The claims in US Patent 4,816,567 do not specifically teach immunoglobulin expression on different vectors or on the same vector wherein the plasmid vector is pBR322 or obtaining the heavy and light chain immunoglobulin variable domains from at least one hybridoma or immunoglobulin expression in mammalian, bacterial (i.e., E. coli strain X1776) and yeast host cells or recovering the immunoglobulin produced in insoluble form (i.e., inclusion bodies) and subsequent solubilization and refolding in solution to form functional immunoglobulin molecules or an anti-CEA antibody or gamma heavy chains and kappa light chains or insoluble particles of heavy and light chains produced in E. coli or yeast or the attachment of a label or drug to the produced immunoglobulin. These

[6] The Examiner states that claims 1-7 of the '567 patent "are also drawn to recombinant processes, vectors and host cells for producing immunoglobulins..." (emphasis added) (Office Action, page 4). However, the referenced claims of the '567 patent do not specify that the result of the process recited by those claims is an immunoglobulin. Instead, these claims plainly state that the result of the process is an individual heavy or light chimeric immunoglobulin chain.

deficiencies are made up for in the teachings of Axel et al and Rice et al and Kaplan et al and Accolla et al. (Emphasis added)

Thus, according to what the Examiner has set forth in the Office Action:

- claims 1, 13, 15-18, 21 and 33 of the '415 patent are rejected solely in view of claims 1, 2, 5, 6 and 7 of the '567 patent, without reference to any other patent or printed publication; and
- claims 2-12, 14, 19, 20, 22-32, and 34-36 of the '415 patent recite features or elements not found in claims 1, 2, 5, 6 and 7 of the '567 patent, but which the Examiner believes are made obvious by other patents or printed publications. [7]

Accordingly, Owners will first respond to the rejections of claims 1, 13, 15-18, 21 and 33 of the '415 patent based on species-genus anticipation. Owners will then address the teachings of the cited patents and printed publications. Finally, Owners will respond to the rejections of dependent claims 2-12, 14, 19, 20, 22-32, and 34-36 in view of the cited patents and printed publications.

B. Observations on the Inventions Defined by the Claims of the '567 and '415 Patents

1. Claims of the '567 Patent Encompass Embodiments that Have an Independent and Distinct Utility Relative to Embodiments Encompassed by Claims of the '415 Patent

During the interview, the Examiners raised general questions regarding the relationship between the inventions defined by the '567 and '415 patents. For example, the Examiners asked whether the processes and compositions of the '567 patent had any purpose other than to produce the immunoglobulin molecules and immunologically functional fragments that result from the processes of the '415 patent claims.

The Examiner is invited to review the enclosed declaration of Dr. Arthur D. Riggs under 37 C.F.R. § 1.132 ("Riggs Declaration"). Dr. Riggs is one of the inventors of the '415 and '567 patents. As he explains, embodiments within the scope of only the '567 patent claims have distinct and unique practical applications relative to embodiments within the

[7] Owners note that the Examiner has rejected dependent claims 11, 12 and 14 of the '415 patent, but has provided no explanation for these rejections. The Examiner does not suggest that these claims are anticipated by a "species" claim of the '567 patent. Nor does the Examiner identify any prior art that, when taken in view of any claim of the '567 patent, would have suggested to a person of skill in the art that these claimed inventions were obvious.

scope of only the '415 patent, and vice versa. These observations are consistent with the multiple determinations by PTO Examiners and the Board that the inventions defined by the two sets of claims are independent and distinct, and thus, separately patentable.

The claims of the '415 patent are generally directed to inventions which require the production in a single host cell of both heavy and light immunoglobulin chains, or fragments comprising at least the variable domains of the heavy and light immunoglobulin chains. The '415 patent claims also require steps that result in the formation of an immunoglobulin molecule or an immunologically functional fragment of an immunoglobulin from independently expressed heavy and light chains.

The inventions defined by the claims of the '567 patent, on the other hand, recite the production of only a heavy or a light chimeric immunoglobulin chain in a host cell. These claims do not require that additional steps be performed. In particular, they do not require both heavy and light chimeric chains to be produced in a single host cell, or that an immunoglobulin molecule or fragment be produced. As such, the "end result" of these processes can be a single chimeric heavy or light immunoglobulin chain. This is not the same end result required by the '415 patent. Stated another way, the '415 patent claims cannot be read to result in a single immunoglobulin heavy or light chain (chimeric or otherwise). Thus, there are embodiments of the '567 patent claims that are not within the scope of or required by the '415 patent claims.

As Dr. Riggs explains, at the time of the invention, a process for producing an individual chimeric immunoglobulin heavy or light chain in a single host cell would provide a reliable and efficient way of obtaining an essentially homogenous composition of an individual chimeric heavy or light immunoglobulin chain. These homogeneous compositions were useful, inter alia, in raising monospecific antisera that selectively bound to individual isotypes of heavy or light immunoglobulin chains. Monospecific antisera raised using individual immunoglobulin chain compositions purified from naturally occurring sources were, at the time of the invention, widely used in clinical diagnostic and research settings. For example, monospecific antisera to specific types of immunoglobulin light chains were used to clinically diagnose and monitor multiple myeloma (e.g., by detecting the presence and quantity of excessive free native kappa or lambda immunoglobulin light chain in urine

samples obtained from a patient). Monospecific antisera also were widely used to characterize and study immunoglobulin structure and function.

That compositions of individual immunoglobulin chains and monospecific antiserum preparations of the nature described above had a well-accepted practical application in 1983 is evidenced by the fact that both such preparations from naturally occurring sources were sold commercially. Copies of catalogs from such suppliers referenced in Dr. Riggs's declaration illustrate this point. See, Riggs Declaration, Exhibit B.

As Dr. Riggs explains, the processes claimed in the '567 patent provide an efficient way to obtain a homogenous composition of an individual chimeric immunoglobulin chain, free of other types of the light or heavy chains and intact immunoglobulins. See, Riggs Declaration, paragraphs 21-31. The processes claimed in the '567 patent, and not those claimed in the '415 patent, provide a direct and efficient route for preparing these homogeneous heavy or light chimeric immunoglobulin chain compositions.

Dr. Riggs also points out that processes for producing individual chimeric heavy or light immunoglobulin chains offer particular advantages for certain "protein-level" manipulations described in the patent. See, Riggs Declaration, paragraphs 4-18. The patent explains (e.g., col. 4, lines 56-62) that protein-level manipulations are processes where immunoglobulin heavy or light chains are manipulated outside of the host cell that has produced each chain. Producing individual heavy or light chains in separate cultures is the most direct and efficient path to compositions of "pure" heavy or light chimeric immunoglobulin chains (i.e., free of the other chain, even in trace amounts). Such purified compositions can then be selectively combined to assemble particular desired immunoglobulins through the protein-level manipulations described in the patent.

As Dr. Riggs observes, the '567 patent disclosure directs researchers to produce certain types of immunoglobulins, particularly "hybrid" antibodies, "univalent" antibodies, and "composite immunoglobulins" by producing the heavy and light immunoglobulin chains in different host cell cultures, and then combining the separately produced chains through protein-level manipulations outside of the cell cultures producing each chain.[8] All of these

[8] "Hybrid" antibodies are antibodies that bind to two distinct antigens resulting from the selective combination of two pairs of heavy and light chains, each pair having specificity for a different antigen. See, column 14, line 64 to column 15 line 9 of the '415 patent and Riggs Declaration, paragraphs 10 to

observations on the relative benefits of processes using individually produced immunoglobulin chains (corresponding to the '567 patent) over processes in which both chains are produced in one host cell (corresponding to the '415 patent) are plainly and clearly reflected in the patent specification.

The distinct character and independent utility of the processes and end products of the respective claims of the '415 and '567 patents reinforces the independent and distinct nature of the inventions claimed in these two patents. These observations also reinforce the fact that the processes and end products of the '567 patent claims are not useful solely for producing the products resulting from the claimed processes of the '415 patent.

2. The '567 Patent Claims Do Not Require Antigen Binding Functionality

During the interview, the Examiners asked Owners to explain the meaning of the phrase "... chimeric immunoglobulin heavy or light chain having specificity for a particular known antigen ..." as is used in the claims of the '567 patent. In particular, they asked whether this phrase, as used in the claims of the '567 patent, means that the recited chimeric chain must be incorporated into an immunoglobulin molecule or an immunologically functional fragment that exhibits antigen binding function.

The Examiner is invited to review the Declaration of Dr. Timothy John Roy Harris under 37 C.F.R. § 1.132 ("Harris Declaration"). Dr. Harris explains in paragraph 12 of his declaration that, by early April of 1983:

> ... the physical structure and biological functions of immunoglobulins were fairly well known. The description of immunoglobulin structure in the '567 and '415 patents (e.g., '415 patent, col. 3, line 17 to col. 4, line 5) is consistent with what was generally understood about immunoglobulin structure and function. By this time, it also was accepted that the antigen binding function of immunoglobulins was associated with the variable domains of the heavy and light chain polypeptides, and that an individual

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13. "Univalent" antibodies are constructs where a heavy and light chain pair are combined with a fragment of the heavy chain. See, column 15, line 49 to column 16, line 2 of the '415 patent and Riggs Declaration, paragraphs 13 to 15. "Composite" immunoglobulins are combinations of heavy and light chains having different antigen binding specificities. See, col. 14, lines 45 to 50 and Riggs Declaration, paragraphs 16-18.

> heavy or light chain polypeptide ordinarily would not bind to antigen very well, if at all.

He then explains in paragraph 13 of his declaration:

> I would rely on this general understanding of immunoglobulin structure and function to answer the question of what the phrase "having specificity for a particular known antigen" means as it is used in the claims of the '567 patent. I view that phrase as it is used in the claims of the '567 patent as referring to amino acid sequences within the variable domain of the individual chimeric heavy chain or light chain polypeptide that confer antigen binding specificity. In such a chimeric polypeptide, these sequences would be derived from the variable domains of an antibody or an antibody fragment exhibiting an antigen binding function.

Thus, as used in the claims of the '567 patent, the phrase "having specificity for a particular known antigen" does not mean that the individual chimeric immunoglobulin chain must exhibit – by itself – antigen binding functionality, or that the chimeric chain must be incorporated into an immunoglobulin molecule or immunologically functional fragment comprising at least the variable domains of the heavy and light chains. See, Harris Declaration, paragraph 14. In part, this is because the claims of the '567 patent plainly cover embodiments limited to a single heavy or light chimeric immunoglobulin chain polypeptide.

C. The Claims of the '415 and '567 Patents Are Not Related as Genus and Species

As noted above, the Examiner relies on only one theory in the Office action to support the rejection of claims 1, 13, 15-18, 21 and 33 of the '415 patent over claims 1, 2, 5, 6 and 7 of the '567 patent, namely, his view that the '415 patent claims define genus inventions which each include a "species" invention defined in the '567 claims. A correct analysis of the claims at issue demonstrates that they are not related as genus and species, and may not be properly rejected for obviousness-type double patenting.

1. Claim 1 of the '415 Patent Does Not Define a "Genus" That Includes a "Species" Defined by Claim 1 of the '567 Patent

Claim 1 of the '415 patent cannot be interpreted to define a genus that includes a species defined by claim 1 of the '567 patent. As such, claim 1 of the '415 patent is not anticipated by claim 1 of the '567 patent, and the "obviousness-type" double patenting rejection premised on this finding is improper and should be withdrawn.

To establish a prima facie case of obviousness-type double patenting based on the "species-genus" theory articulated in the Office Action, the Examiner must show that the two claims define processes that exist in a true species-genus relationship. As explained below, they do not.

(a) A Genus Claim Must Fully Encompass the Species Claim

A true "genus-species" relationship requires the putative species to be fully encompassed by the putative genus claim. As § 806.04(d) of the Manual of Patent Examining Procedure (MPEP) observes:

> It is not possible to define a generic claim with that precision existing in the case of a geometrical term. In general, a generic claim should include no material element additional to those recited in the species claims, and must comprehend within its confines the organization covered in each of the species.

See, also, In re Bronson, 168 F.2d 548 (C.C.P.A. 1948)("A generic claim should include no material element in addition to those recited in the species claim, and must comprehend the organization covered in each of the species claims."); Regents of the Univ. of Calif. v. Eli Lilly & Co., 119 F.3d 1559, 1568 (Fed. Cir. 1997)(a genus of cDNA is defined by "a recitation of structural features common to the members of the genus....").[9] Stated another way, by practicing the invention defined by a species claim, one must necessarily infringe the genus claim. If this is not the case, the claims are not related as species and genus.

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[9] See also, 37 C.F.R. § 1.146. Election of species:
In the first action on an application containing a generic claim to a generic invention (genus) and claims to more than one patentably distinct species embraced thereby, the examiner may require the applicant in the reply to that action to elect a species of his or her invention to which his or her claim will be restricted if no claim to the genus is found to be allowable. ...

This logical conclusion flows naturally from the law of anticipation.[10] Courts rely on the law of anticipation when assessing obviousness-type double patenting questions in situations where a first patent claims a species that is wholly included in the scope of a later issuing patent claim defining a genus. See, e.g., In re Berg, 140 F.3d 1428, 1437 (Fed. Cir. 1998) (affirming a holding of obviousness-type double patenting where a patent application claim to a genus was anticipated by a patent claim to a species within that genus); In re Van Ornum, 686 F.2d 937 (C.C.P.A. 1982); In re Braithwaite, 379 F.2d 606 (C.C.P.A. 1967); In re Lonardo, 119 F.3d 960 (Fed. Cir. 1997). Specifically, it is based on cases which find that a claim defining a genus is anticipated by the prior disclosure of a species wholly included within that genus claim. See, M.P.E.P. §2131.02. See also, Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342 (Fed. Cir. 1999) ("In chemical compounds, a single prior art species within the patent's claimed genus reads on the generic claim and anticipates it."); In re Gosteli, 872 F.2d 1008, 1010 (Fed. Cir. 1989) ("Section 102(e) bars the issuance of a patent if its generic claims are anticipated by prior art disclosing individual chemical species."). It is well settled under the law of anticipation that each claimed element appear identically in the prior art disclosure. See, Gechter v. Davidson, 116 F.3d 1454, 1457 (Fed. Cir. 1997)(to establish anticipation under §102, "every limitation of a claim must identically appear in a single prior art reference.").

(b) Analysis Must Be Based on a Comparison of Each Claim Considered as Whole

A double-patenting analysis must be based on a comparison of each claim considered as a whole. See, e.g., General Foods Corp. v. Studiengesellschaft Kohle mbH, 972 F.2d 1272, 1278-79 (Fed. Cir. 1992)("Claims must be read as a whole in analyzing a claim of double patenting."); Apple Computer, Inc. v. Articulate Systems, Inc., 234 F.3d 14, 25, (Fed. Cir. 2000); Eli Lilly v Barr Laboratories, Inc., 251 F.3d 955, 972 (Fed. Cir. 2001) ("We have compared the differences between the claims at issue as a whole and conclude that they are not patentably distinct.")(emphasis added). In other words, the processes as defined by all the

[10] "A century-old axiom of patent law holds that a product 'which would literally infringe if later in time anticipates if earlier.'" Upsher-Smith Labs., Inc. v. Pamlab, L.L.C., 412 F.3d 1319, 1322 (Fed. Cir. 2005). Thus, if a species would anticipate a generic claim, that species would also infringe that claim. See In re Slayter, 125 U.S.P.Q. 345 (C.C.P.A. 1960) (a genus or subgenus claim reads on a species); In re Smith, 458 F.2d 1389 (C.C.P.A. 1972) (characterizing a genus as encompassing a subgenus, and the subgenus as reading on a species).

required steps of claim 1 of the '567 patent must be compared to the process defined by all the required steps of claim 1 of the '415 patent.

It is improper to compare only one step or element found in both of the claims and to ignore additional steps required by claim 1 of the '415 patent. Similarly, it is improper to ignore the end results of the two processes, which plainly are different (i.e., the '415 claims require the result to be immunoglobulin molecules or fragments that have light and heavy chain components, while the '567 claims requires only a single heavy or light chimeric immunoglobulin chain).

(c) Comparison of Claim 1 of the '567 Patent to Claim 1 of the '415 Patent

Table 1 shows a side-by-side comparison of claim 1 of the '415 patent to claim 1 of the '567 patent. The table illustrates through underlining which of the corresponding elements in the two claims are "narrower" (i.e., which encompass a narrower scope of subject matter).

Table I. Comparison of Claim 1 of the '415 Patent to Claim 1 of the '567 Patent

'567 patent (claim 1)	'415 patent (claim 1)
1. A method comprising	1. A process for producing an immunoglobulin molecule or an immunologically functional immunoglobulin fragment comprising at least the variable domains of the immunoglobulin heavy and light chains in a single host cell comprising the steps of:
(a) preparing a DNA sequence encoding a chimeric immunoglobulin heavy or light chain having specificity for a particular known antigen wherein a constant region is homologous to the corresponding constant region of an antibody of a first mammalian species and a variable region thereof is homologous to the variable region of an antibody derived from a second, different mammalian species;	(i) transforming said single host cell with a first DNA sequence encoding at least the variable domain of the immunoglobulin heavy chain and a second DNA sequence encoding at least the variable domain of the immunoglobulin light chain, and
(b) inserting the sequence into a replicable expression vector operably linked to a suitable promoter compatible with a host cell; (c) transforming the host cell with the vector of (b); (d) culturing the host cell; and (e) recovering the chimeric heavy or light chain from the host cell culture	(ii) independently expressing said first DNA sequence and said second DNA sequence so that said immunoglobulin heavy and light chains are produced as separate molecules in said transformed single host cell.

(d) Claim 1 of the '415 Patent Includes Material Elements Not Required by Claim 1 of the '567 Patent

It is immediately apparent from an inspection of these claims that the process defined by claim 1 of the '415 patent requires additional steps that are not required by the process claim 1 of the '567 patent. Specifically:

- claim 1 of the '415 patent requires that the process result in an "immunoglobulin molecule or an immunologically functional immunoglobulin fragment" while claim 1 of the '567 patent requires no such result (i.e., it only requires the process to result in a chimeric immunoglobulin heavy or light chain); and

- claim 1 of the '415 patent requires that two polypeptides be independently expressed in a single host cell (i.e., the heavy and light immunoglobulin chains or portions thereof necessary to yield the recited immunoglobulin molecules or immunologically functional fragments), whereas the '567 patent requires only one immunoglobulin chain to be expressed in a single host cell.

The additional steps implicated by these limitations include (i) that the host cell be transformed with an additional DNA sequence, (ii) that the transformed host cell be cultured so as to independently express two, rather than one immunoglobulin polypeptide, and (iii) that steps be taken that result in the association of the individually expressed heavy and light immunoglobulin into an immunoglobulin molecule or an immunologically functional immunoglobulin fragment.

Plainly, the additional steps that must be performed pursuant to claim 1 of the '415 process are "material elements" of this process claim that are not found in claim 1 of the '567 patent. Similarly, the requirement that the process defined in claim 1 of the '415 patent result in an immunoglobulin molecule or an immunologically functional fragment is a material element of the claim that is not found in claim 1 of the '567 patent.

(e) Claim 1 and 13 of the '415 Patent Can be Infringed Without Necessarily Infringing Claim 1 of the '567 Patent and Vice Versa

Because claim 1 of the '415 patent includes additional material elements not found in claim 1 of the '567 patent, a person performing the steps of the putative "species" process of claim 1 of the '567 patent will not necessarily infringe the putative genus process defined by claim 1 of the '415 patent. For example, a person producing only one immunoglobulin heavy or light chain will not perform all of the steps required by claim 1 of the '415 patent, would

not obtain an immunoglobulin molecule or an immunologically functional immunoglobulin fragment having both heavy and light chain elements, and thus would not literally infringe the '415 patent. Similarly, a person who produces heavy and light immunoglobulin chains in separate host cells will not literally infringe the claims of the '415 patent, even if those separately produced chains are later combined to form an immunoglobulin molecule or immunologically functional fragment.

It is also possible for a person to practice embodiments falling within the scope of claim 1 of the '415 patent without necessarily infringing claim 1 of the '567 patent. For example, a person producing a non-chimeric heavy and light chain immunoglobulin molecule in a single host cell will not infringe claim 1 of the '567 patent.

Because one can perform all of the steps required by claim 1 of the '567 patent without necessarily infringing claim 1 of the '415 patent, and vice versa, these claims plainly are not related as species and genus (or genus and species). Similarly, claim 13, which depends from claim 1 of the '415 patent, specifies that for either the light or heavy chain DNA sequence, the variable region and constant region are from different species.[11] For the same reasons that claim 1 of the '415 patent is not a genus of claim 1 of the '567 patent, claim 13 is also not a genus.

(f) Domination is Irrelevant to an Obviousness-Type Double Patenting Analysis

Owners also note that the Examiner makes certain observations regarding the scope of claim 1 of the '567 patent and claim 1 of the '415 patent that confuse the analysis. Specifically, the Examiner finds that claim 1 of the '567 patent "reads on" and thus dominates processes that are also covered by claim 1 of the '415 patent. The Examiner points, in particular, to the open claim language ("comprising") used in claim 1 of the '567 patent. By doing so, the Examiner erroneously concludes that "domination" is somehow relevant to a double patenting analysis.

It is legally irrelevant to a double-patenting analysis whether certain conduct would be "dominated" by two patents. See, e.g., In re Kaplan, 789 F.2d 1574, 1577 (Fed. Cir.

[11] The '567 patent requires a chimeric heavy or light chain DNA sequence in which the variable and constant regions are from different mammalian species.

1986)("Domination is an irrelevant fact.")[12] Moreover, "it is elementary that readability of a claim on the subject matter of another claim (domination) is neither determinative of the double patenting issue nor demonstrative that claims are directed to the same invention." In re Sarett, 327 F.2d 1005, 1014 (C.C.P.A. 1964); see also General Foods Corp., 972 at 1278-79. Thus, "'domination'...by itself, does not give rise to 'double patenting.'" Kaplan, 789 F.2d at 1577. Furthermore, "[i]t is basic patent law that claims of a patent may dominate those of an application yet that is not necessarily determinative of whether the invention defined in the application is obvious in view of the teachings set forth in the prior art patent." In re Ornitz, 376 F.2d 330, 335 (C.C.P.A. 1967); Kaplan, 789 F.2d at 1577.

As MPEP § 804 explains:

> Domination and double patenting should not be confused. They are two separate issues. One patent or application "dominates" a second patent or application when the first patent or application has a broad or generic claim which fully encompasses or reads on an invention defined in a narrower or more specific claim in another patent or application. Domination by itself, i.e., in the absence of statutory or nonstatutory double patenting grounds, cannot support a double patenting rejection. In re Kaplan, 789 F.2d 1574, 1577-78, 229 USPQ 678, 681 (Fed. Cir. 1986); and In re Sarrett, 327 F.2d 1005, 1014-15, 140 USPQ 474, 482 (CCPA 1964). However, the presence of domination does not preclude double patenting. See, e.g., In re Schneller, 397 F.2d 350, 158 USPQ 210 (CCPA 1968)."

Similarly, the fact that claims in one patent may "read on" certain subject matter that is specifically claimed in a second patent does not establish that the two claims exist in a

[12] See, Kaplan at 1577-78 ("By domination we refer, in accordance with established patent law terminology, to that phenomenon, which grows out of the fact that patents have claims, whereunder one patent has a broad or "generic" claim which "reads on" an invention defined by a narrower or more specific claim in another patent, the former "dominating" the latter because the more narrowly claimed invention cannot be practiced without infringing the broader claim. To use the words of which the board seemed to be enamored, the broader claim "embraces" or "encompasses" the subject matter defined by the narrower claim. In possibly simpler terms, one patent dominates another if a claim of the first patent reads on a device built or process practiced according to the second patent disclosure. This commonplace situation is not, per se, double patenting as the board seemed to think.") The court, in Kaplan, also quoted E. Stringham's 1933 treatise: "[o]ne of the simplest, clearest, soundest, and most essential principles of

"genus-species" relationship. The MPEP provides the following example to illustrate how a genus claim can be distinguished from a "dominating" claim:

> In an application presenting three species illustrated, for example, in Figures 1, 2, and 3, respectively, a generic claim should read on each of these views; but the fact that a claim does so read is not conclusive that it is generic. It may define only an element or subcombination common to the several species. (emphasis added)

See, MPEP § 806.04(d).

The Examiner's observations that claims of both the '415 and '567 patents may be infringed by certain third party conduct thus provide no relevant insight into the question of obviousness-type double patenting of the claims of these two patents. Instead, as explained above, the proper comparison is between the inventions that are defined by the entirety of claim 1 of the '415 patent relative to the inventions that are defined by the entirety of claim 1 of the '567 patent.

Accordingly, claim 1 of the '415 patent is not a "genus" process that includes within its scope the process defined by claim 1 of the '567 patent. As such, claim 1 of the '567 patent does not anticipate claim 1 of the '415 patent. The obviousness-type double patenting rejection of claim 1 of the '415 patent based on this premise thus is plainly improper and should be withdrawn.

2. Claim 21 of the '415 Patent Does Not Define a "Genus" That Includes a "Species" Defined by Claim 1 of the '567 Patent

As was the case for claim 1 of the '415 patent, claim 21 of the '415 patent does not define a "genus" of processes that includes the process defined by claim 1 of the '567 patent. Table 2 in Exhibit E provides a side-by-side comparison of claim 21 of the '415 patent to claim 1 of the '567 patent.

Claim 21 of the '415 patent more closely parallels the form of claim 1 of the '567 patent. The distinctions in scope between the respective elements of the two claims,

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patent law, is that a later invention may be validly patented, although dominated by an earlier patent, whether to the same or to a different inventor."

however, are even more immediately apparent. Specifically, claim 21 of the '415 patent requires:

- preparation of a DNA sequence encoding both a heavy and a light immunoglobulin chain or a Fab region (i.e., comprising those portions of the heavy and light chains necessary to yield a Fab region);
- transformation of a prokaryotic or eukaryotic microbial host cell, rather than any host cell; and
- recovery of an immunoglobulin that is capable of binding to a known antigen.

Thus, several elements of claim 21 of the '415 patent are narrower than corresponding elements of claim 1 of the '567 patent. Claim 21 of the '415 also requires the practicing of additional steps relative to claim 1 of the '567 patent. As such, claim 21 is not a "genus" claim that includes within its scope the "species" defined by claim 1 of the '567 patent, and claim 21 is not anticipated by claim 1 of the '567 patent. A rejection for double-patenting predicated on this basis is thus plainly improper and should be withdrawn.

3. Claim 33 of the '415 Patent Does Not Define a "Genus" That Includes a "Species" Defined by Claim 1 of the '567 Patent

Claim 33 of the '415 patent defines a process comparable in form to claim 1 of the '415 patent. This claim, for reasons similar to those set forth above regarding claim 1 of the '415 patent, does not define a "genus" of processes that includes the process defined by claim 1 of the '567 patent. Table 3 in Exhibit E provides a side-by-side comparison of claim 33 of the '415 patent to claim 1 of the '567 patent.

As was the case with claim 1 of the '415 patent, it is immediately apparent that claim 33 of the '415 patent – considered in its entirety – requires additional steps that are not required by the process claim 1 of the '567 patent. Specifically:

- claim 33 of the '415 patent requires that the process result in an "immunoglobulin molecule or an immunologically functional immunoglobulin fragment";
- claim 33 of the '415 patent requires that two polypeptides be individually produced in a single host cell that has been transformed to include DNA sequences encoding both the heavy and light immunoglobulin chains (i.e., the heavy and light immunoglobulin chains or portions thereof necessary to yield the recited immunoglobulin molecules or immunologically functional fragments).

Claim 33 of the '415 patent also specifies that the heavy and light immunoglobulin chain DNA sequences must be independently expressed in the host cell. This further distinguishes claim 33 from the process defined by claim 1 of the '567 patent.

As was the case with claims 1 and 21 of the '415 patent, claim 33 of the '415 patent does not define a "genus" that includes the "species" defined by claim 1 of the '567 patent, and is not anticipated this claim. This conclusion is compelled because (i) claim 33 includes material limitations not recited in claim 1 of the '567 patent, and (ii) several elements in claim 33 of the '415 patent are narrower than corresponding elements in claim 1 of the '567 patent. Thus, the rejection for double-patenting is plainly improper and should be withdrawn.

4. Claims 15-17 of the '415 Patent Do Not Define a "Genus" That Includes a "Species" Defined by Claim 5 of the '567 Patent

Claim 15 of the '415 patent is directed to a vector comprising a first DNA sequence encoding at least a variable domain of an immunoglobulin heavy chain, and a second DNA sequence encoding at least a variable domain of an immunoglobulin light chain. In contrast, claim 5 of the '567 patent is directed to a replicable expression vector comprising at least one DNA sequence encoding a chimeric immunoglobulin heavy or light chain. Table 4 in Exhibit E provides a side-by-side comparison of these claims.

Claim 16 further limits claim 15 by requiring the vector to be a plasmid. Claim 17 is directed to a host cell transformed with a vector defined by claim 15. Since the Examiner has not differentiated his rationale for finding claims 16 and 17 to be genus claims relative to claim 5 of the '567 patent, Owners will simply focus on the relationship between claim 15 of the '415 patent and claim 5 of the '567 patent.

As was the case with the process claims of the '415 patent, claim 15 of the '415 patent does not define a "genus" of compounds that by necessity includes "species" of vectors defined by claim 5 of the '567 patent. Specifically, claim 15 requires that the vector include at least two distinct DNA sequences: one encoding a heavy chain, and one encoding a light chain. Claim 15 of the '415 patent also includes an additional material limitation relative to claim 5 of the '567 patent; namely, that the two DNA sequences must be located in the vector at different insertion sites.

Plainly, there are embodiments falling within the scope of only claim 5 of the '567 patent (e.g., vectors containing a DNA sequence encoding only a heavy or a light chimeric chain, but not both) and not claim 15 of the '415 patent. For example, a person who makes a vector containing a DNA sequence encoding only a heavy or a light chimeric immunoglobulin chain would not literally infringe claim 15 of the '415 patent. And, simply because one feature of claim 15 of the '415 patent is broader (i.e., chimeric and non-chimeric) than its counterpart in the '567 patent (i.e., only chimeric) does not transform claim 15 of the '415 patent into a "generic" claim relative to claim 5 of the '567 patent. In view of these observations, this rejection is plainly improper and should be withdrawn.

5. Claim 18 of the '415 Patent Does Not Define a "Genus" That Includes a "Species" Defined by Claim 7 of the '567 Patent

Claim 18 of the '415 patent is directed to host cells transformed with two distinct vectors, a first containing a DNA sequence encoding an immunoglobulin heavy chain, and the second containing a DNA sequence encoding an immunoglobulin light chain. In contrast, claim 7 of the '567 patent is directed to a host cell transformed with the vector defined by claim 5 of the '567 patent (i.e., a replicable expression vector comprising one DNA sequence encoding a chimeric immunoglobulin heavy or light chain). Table 5 in Exhibit E provides a side-by-side comparison of these claims.

As was the case with the vector claims of the '415 patent, claim 18 of the '415 patent does not define a "genus" of host cells that includes the "species" of host cell defined by claim 7 of the '567 patent. Specifically, claim 18 requires transforming a host cell with at least two distinct vectors. Each of the vectors must include a DNA sequence encoding at least the variable domain of a heavy or a light immunoglobulin chain. In contrast, the host cell defined by claim 7 of the '567 patent requires only a single vector containing either a DNA sequence encoding a chimeric heavy chain or one encoding a chimeric light chain.

Because claim 18 of the '415 patent defines an article of manufacture (i.e., a transformed host cell) requiring at least two elements. namely, at least two vectors, it cannot be portrayed as being "generic" to a claim requiring only one of those two elements. And, again, simply because one element of claim 18 of the '415 patent is "broader" (i.e., including both chimeric and non-chimeric) than a corresponding element of claim 7 of the '567 patent (i.e., limited to chimeric) does not transform this claim into a "generic" claim relative to

claim 7 of the '567 patent: Plainly, a person can practice embodiments within the scope of claim 7 of the '567 patent (e.g., a host cell transformed with DNA sequence encoding only a heavy or a light chimeric immunoglobulin chain) that do not fall within the scope of claim 18 of the '415 patent.

In view of these observations, this rejection is plainly improper and should be withdrawn.

E. The Examiner Has Not Established a Prima Facie Case that Claims 2-12, 14, 19, 20, 22-31 and 33-36 are Unpatentable for Obviousness-Type Double Patenting

In an obviousness-type double patenting analysis, the Examiner must compare what is defined by the claims of the later patent against what is defined by the claims of the earlier patent. This analysis must be based on the claims as a whole, not one feature or element of the claims considered in isolation. A prima facie showing of obviousness-type double patenting must explain why the invention defined by the earlier issued claims renders obvious the invention defined by later issued claims.

The Examiner has not explained why the inventions defined by claims 1, 13, 15-18, 21 and 33 would be considered "obvious" in view of the inventions defined by the recited claims of the '567 patent. The only rationale offered by the Examiner for the rejection is the incorrect assumption that the '415 patent claims each define a genus of inventions that includes and is thus anticipated by species defined by the referenced claims of the '567 patent. Because that assumption is incorrect, the Examiner's rejection of claims 1, 13, 15-18, 21 and 33 of the '415 patent over claims 1, 3, 5, 6 and 7 of the '567 patent is improper and should be withdrawn.

The Examiner has also rejected the remaining dependent claims of the '415 patent. Each of those additional rejections is based on the assumption that claims 1, 13, 15-18, 21 and 33 of the '415 patent are anticipated by claims 1, 3, 5, 6 and 7 of the '567 patent. This (incorrect) assumption is acknowledged by the Examiner to be insufficient to reject claims 2, 12, 14, 19, 20-22, 31, 32 and 34-36, standing alone. The Examiner cites a variety of additional patents and printed publications to suggest that the additional limitations of these

claims, while being sufficient to preclude a finding of "anticipation," nonetheless are obvious variations of the earlier "species" claims of the '567 patent.

Since these additional rejections rest on an incorrect premise (i.e., anticipation of the independent claims), the Examiner has not set forth a prima facie showing that these claims are unpatentable for reasons of obviousness-type double patenting. Moreover, for reasons provided below, the Examiner has not and cannot establish a prima facie showing of obviousness of these claims based on the cited patents and printed publications.

1. General Observations on Axel

During the interview held on October 25, 2005, the Examiners requested that Owners discuss the Axel patent, and its relevance to the claims of the '415 patent, particularly whether the '567 patent claims, taken in view of Axel, would render the claims of the '415 patent claims "obvious."

Initially, Owners note that the rejection of claims 1, 13, 15-18, 21 and 33 of the '415 patent, as expressed in the Office Action, is in no way based on Axel. It is difficult to address any perceived relevance of Axel to these claims absent a specific explanation from the Office why these claims would have been considered obvious over one or more claims of the '567 patent taken in view of Axel. And the only general discussion of Axel by the Examiner appears at page 5 of the Office Action. This passage reads:

> Axel et al teaches a process for inserting foreign DNA into eukaryotic cells by co-transforming the cells with this foreign DNA and an unlinked DNA that codes for a selectable phenotype not otherwise expressed by the cell (See column 3, lines 21-27). Axel describes the process as particularly suited for the transformation of DNA into eukaryotic cells for making immunoglobulins (See column 3, lines 31-36). Axel thus demonstrates the predictability of expression of multiple heterologous proteins in a single host cell. Axel also suggests the desirability of expressing immunoglobulins in mammalian host cells, and as intact (assembled) proteins.

Owners submit this does not accurately reflect the teachings of Axel, nor does it convey their potential relevance to the present claims.

The Examiner is invited to review the accompanying Harris Declaration, particularly paragraphs 20-30. As Dr. Harris explains, Axel does not suggest processes for producing and isolating multiple different polypeptides from a transformed host cell. Instead, Axel describes a method in which a eukaryotic cell is co-transformed with a first DNA sequence (i.e., "DNA I" encoding a "proteinaceous material" that is produced by and isolated from the transformed host cell) and a second DNA sequence (i.e., "DNA II" encoding a selectable marker that is not isolated from the transformed host cell). The Axel process envisions that only one "proteinaceous material" (i.e., that encoded by DNA I) will be produced by and isolated from the transformed cell.

The Examiner's attention in this regard is directed to Figure 1 of Axel, which provides an overview of the Axel process. Figure 1 explains that "DNA I coding for desired proteinaceous material" and "DNA II coding for selectable marker" are introduced into the host cell through co-transformation. As described in Figure 1, only the "desired proteinaceous material" encoded by DNA I is ultimately isolated from the cell. The role of "DNA II" is to introduce a selectable marker into the cell so that cells that successfully express the introduced DNA II sequence can be readily identified and differentiated from those in which the introduced DNA II sequence is not expressed. Indeed, for the "selectable marker" to function for its intended purpose according to Axel, it must not be isolated from the cell – otherwise the cell would lose its ability to be influenced by the introduction into the culture medium of an agent that facilitates the selective removal of cells that are not expressing introduced DNA II.

A person of skill, following the explicit guidance in Axel, would not introduce a "second" DNA sequence (DNA II) encoding something incapable of introducing a selectable trait into the transformed cell. See, Harris Declaration, paragraph 24. Certainly, Axel does not suggest that an immunoglobulin light or heavy chain can serve as a "selectable marker" encoded by DNA II. A DNA sequence encoding an immunoglobulin chain thus would not be used as "DNA II" according to the Axel process.

The Axel disclosure also does not suggest that a third DNA sequence should be introduced into the cell along with DNA I and DNA II (i.e., a "DNA III" corresponding to a second polypeptide to be produced by and ultimately isolated from the transformed cell). See, Harris Declaration, paragraph 25. Instead, as explained by Dr. Harris, the Axel patent

describes a two-DNA system, with one DNA (i.e., DNA I) encoding the polypeptide ultimately isolated from the cell, and a second DNA (i.e., DNA II) being used to transform the cell to contain a selectable marker. See, Harris Declaration, paragraphs 21-22.

The law is settled that if modifications of a prior art reference necessary to yield the claimed invention would render the prior art's teachings inoperative, that prior art teaches away from the claimed invention and cannot be used to support a finding of obviousness. See, e.g., Tec-Air, Inc. v. Denso Manufacturing, Inc., 192 F.3d 1353, 1360 (Fed. Cir. 1999), in which the Federal Circuit held:

> There is no suggestion to combine, however, if a reference teaches away from its combination with another source. See id. at 1075, 5 USPQ2d at 1599. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant ... [or] if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." In re Gurley, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). If when combined, the references "would produce a seemingly inoperative device," then they teach away from their combination. In re Sponnoble, 56 C.C.P.A. 823, 405 F.2d 578, 587, 160 USPQ 237, 244 (1969); See also In re Gordon, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984) (finding no suggestion to modify a prior art device where the modification would render the device inoperable for its intended purpose). (emphasis added)

Here, it is essential to the Axel process that "DNA II" encode a selectable marker. Changing DNA II in Axel to encode the second chain of an immunoglobulin (i.e., where DNA I encodes a first immunoglobulin chain) would result in transformed cells lacking a selectable marker within the meaning of Axel. Such transformed cells thus would be inoperative for the purposes described as being essential to the Axel patent process.

Owners also note that contrary to the Examiner's suggestion, certain passages in Axel cited by the Examiner do not suggest or imply that genes encoding two distinct polypeptides

may be introduced into, expressed by, and ultimately isolated from transformed eukaryotic host cells. For example, the Examiner cites column 6, lines 44-66 of Axel. As is immediately apparent from this passage of Axel, the reference to "multiple copies" is a reference to multiple copies of the same DNA I and DNA II sequences. Thus, as the quoted passage points out:

> One process for inserting a multiplicity of foreign DNA I molecules into a eucaryotic cell comprises cotransforming the cell with multiple DNA I molecules and with multiple, unlinked foreign DNA II molecules corresponding to multiple copies of an amplifiable gene for a dominant selectable phenotype not otherwise expressed by the cell. This cotransformation process is carried out in a suitable medium and in the presence of an agent permitting survival and/or identification of cells which acquire the dominant selectable phenotype. Preferably, this is done in the presence of successively higher concentrations of such an agent so that only those cells acquiring the highest number of amplifiable dominant genes (DNA II) survive and/or are identified. These cells then also contain multiple copies of DNA I. This approach is particularly appropriate for the insertion of multiple copies of amplifiable genes which confer drug resistance upon the cell, e.g., the mutant dihydrofolate reductase gene which renders cells resistant to methotrexate. (Emphasis added.)

This passage explains that multiple copies of DNA I and DNA II are introduced to increase the number of copies of DNA I and DNA II that might be successfully incorporated into the cell. Axel reasons that this will lead to a greater likelihood that the two sequences will be successfully expressed. This teaching in Axel does not, as the Examiner seems to imply, suggest the idea of inserting multiple distinct DNA sequences encoding distinct polypeptides that are to be isolated from the transformed cell.

The Axel disclosure also provides no description of procedures for producing immunoglobulin molecules or immunologically functional fragments having both heavy and light chain elements. As Dr. Harris points out, Axel only mentions "antibodies" as one example in a list of possible types of polypeptides that could be produced by the processes

described in Axel. See Harris Declaration, paragraph 26. "Antibodies" are simply not discussed in Axel other than in this context.

The total absence in Axel of any actual description of procedures for producing immunoglobulin molecules or immunologically active fragments through recombinant techniques renders the Axel patent irrelevant to the claims of the '415 patent claims. As Dr. Harris explains, Axel neither suggests nor describes how one would transform a single eukaryotic cell to contain and express genes encoding two distinct polypeptides that are to be ultimately recovered from the transformed cell, much less a heavy and light chain of an immunoglobulin. See, Harris Declaration, paragraphs 25-28.

The Examiner's apparent extrapolations of Axel's teachings are directly contrary to how a person of skill in the art in early April of 1983 would have actually viewed the Axel disclosure. As Dr. Harris observes in paragraph 28 of his declaration:

> I do not agree with the Examiner that the Axel patent suggests the desirability of producing immunoglobulins as "intact (assembled) proteins." I am unable to find any mention in Axel of the desirability of producing "intact (assembled)" immunoglobulins, and nothing in the Axel patent provides any guidance on how to assemble "intact" immunoglobulins.

Indeed, the Axel patent has no disclosure that even generally discusses the concept of producing a multimeric protein having multiple distinct polypeptide constituents by independently expressing genes corresponding to the constituent polypeptides in a single host cell. See, Harris Declaration, paragraphs 25 and 27.

The Axel patent, read properly and accurately, cannot be cited by the Office as teaching what the Examiner suggests it does at page 5 of the Office Action. Specifically, Axel does not describe or suggest in any way the idea of independently expressing DNA sequences encoding heavy and light chains of an immunoglobulin in a single host cell. It certainly does not demonstrate the predictability of producing multiple heterologous proteins that one intends to isolate in a single host cell. And Axel cannot "suggest the desirability of expressing immunoglobulins in mammalian host cells, and as intact (assembled) proteins" because there is literally no discussion of this in the Axel patent.

The Examiner is also reminded that the teachings of the '567 patent claims may not be used to support a double-patenting rejection. See, General Foods 972 F.2d at 1281 ("Our precedent makes clear that the disclosure of a patent cited in support of a double patenting rejection cannot be used as though it were prior art, even where the disclosure is found in the claims" (emphasis in original).) Thus, the Office may not cite the '567 patent claims to suggest that the '567 patent claims "enable" the production of one or more immunoglobulin chains, or that they "suggest" the production of two immunoglobulin chains in a single host cell. Rather, such evidence must come from the prior art used in conjunction with the patent claims at issue. As explained above, Axel provides no such evidence.

Based on these observations, Owners submit that the Office cannot properly reject one or more of the claims of the '415 patent on the basis of the '567 patent taken in view of Axel. As noted above, doing so also would contradict the numerous independent findings of the Board and of different Examiners that the '415 patent claims are not deficient for obviousness-type double patenting over the '567 patent claims. And, Owners submit that such a rejection, if imposed by the Office in the next Office action, would plainly constitute a new ground of rejection that is not stated in the current Office Action.

2. General Observations on Rice

As noted above, the Office does not base its explanation of the rejection of claims 1, 13, 15-18, 21 and 33 of the '415 patent on reasoning that claims of the '567 patent, taken in view of Rice, would have rendered such claims obvious. As was the case with Axel, it is difficult to address any perceived relevance of Rice to these claims in the absence of a specific rationale or explanation of why the Office would consider these claims to have been considered obvious to a person of skill in the art in early April of 1983, based on one or more claims of the '567 patent taken in view of Rice.

At page 6 of the Office Action, the Examiner makes certain remarks on what Rice teaches. Specifically, he states:

> Rice et al successfully introduced a recombinant rearranged murine kappa light chain gene construct into an Abelson murine leukemia virus (A-MuLV)-transformed lymphoid cell line, which is a cell line that already synthesized γ2b heavy chain protein (see page 7862). Rice inserted the

light chain gene into a plasmid, used this plasmid to transfect the cells, and then examined the polypeptides as well as the RNA produced by the cells (see pages 7863-7864, and Figures 2 and 3). Lastly, since the cells were producing both immunoglobulin chains, the cells were examined for the ability to assemble the chains into IgG molecules, leading to the observation that "[e]ssentially all of the K-chain produced in the K-2 cells appears to be assembled into IgG2b." (see page 7864). Thus, at the time of filing the application for the '576 and '415 patent it was known in the art that host cells could express "heavy or light chains," and that expression of both chains was routine, resulting in assembly into immunoglobulins.

The Examiner is invited to consider the Declaration of Dr. Douglas A. Rice under 37 C.F.R. § 1.132 ("Rice declaration"), provided herewith. Dr. Rice is the lead author of the Rice publication cited by the Examiner. As Dr. Rice points out, "[m]y paper does not explain how one might make transfected host cells that produce immunoglobulins formed from the products of independently expressed exogenous heavy and light chain genes." Rice Declaration, paragraph 17. Instead, he explains that his paper reported on research being conducted in his and his co-author's laboratory that was aimed at gaining a better understanding of the mechanisms by which differentiated B cells regulate immunoglobulin expression.

As Dr. Rice explains, his publication describes experiments involving a lymphoid cell line (the 81A-2 line) that was not producing an immunoglobulin light chain, but was producing an endogenous heavy chain. The 81A-2 line was not "engineered" to selectively express only heavy chain, but was derived from a chance mutation of a parent lymphoid cell line. Instead, it was selected because it was relatively mature, and because it was producing a "native" (endogenous) heavy chain. See, Rice Declaration, paragraphs 9 and 10. Dr. Rice transformed this subclone with an exogenous gene encoding an arbitrarily chosen murine κ-light chain. See, Rice Declaration, paragraph 11.

In paragraph 12 of his declaration, Dr. Rice explains that it would have been inappropriate to use the 81A-2 subclone described in his paper to practice the processes claimed in the '415 patent. For example, he points out that the 81A-2 line was already producing heavy chain. In fact, Dr. Rice observes that it never occurred to him to attempt to

express an exogenous light and an exogenous heavy chain gene in the 81A-2 cell line in connection with the experiments described in the Rice paper. See, Rice Declaration, paragraph 13. And Dr. Rice indicates that he was not aware of any other group that was attempting to express exogenous recombinant heavy and light chain genes in a single host cell at the time his paper was published. See, Rice Declaration, paragraph 15.

Dr. Rice specifically disagrees with the Examiner's characterization of what his publication established. As he explains in paragraph 14 of his Declaration:

> The Examiner is incorrect, and I disagree with the suggestion, that by early April 1983, my *PNAS* paper had made routine or predictable the task of expressing exogenous immunoglobulin light and heavy chain genes in the same cell. In later experiments, I attempted to use the techniques described in the *PNAS* paper to introduce and express single Ig genes into other lymphoid cell lines. Most of these experiments failed to produce stable transfectants. Thus, my experience was that using the same transfection and selection conditions described in the *PNAS* paper with other cell lines or other Ig genes did not routinely yield stable transformants containing even a single exogenous Ig gene.

Thus, based on his actual experiences, Dr. Rice holds precisely the opposite of the view held by the Examiner as to what his publication had established in early April of 1983. Dr. Rice makes it clear that the disclosure in his paper did not establish that expression of even one immunoglobulin chain gene was "routine" in early April 1983.

Dr. Rice also directly refutes the Examiner's suggestion that, in early April of 1983, it was known in the art that host cells could express genes encoding exogenous heavy and exogenous light chains and that "expression of both chains was routine, resulting in assembly into immunoglobulins." See, e.g., Rice Declaration, paragraphs 16 and 17. Owners note that such a suggestion by the Examiner would completely ignore the fact that the Rice experiments used a cell line that was already expressing an endogenous (native) heavy chain gene. And, there is absolutely no suggestion in the Rice publication that an exogenous heavy chain gene could or should be inserted into and expressed by the 81A-2 cell line, let alone any other host cell.

Moreover, as Dr. Harris points out, mere knowledge that mature B cells express their endogenous heavy and light chain immunoglobulin genes and assemble the resulting polypeptide chains into immunoglobulin tetramers is essentially irrelevant to the question of whether one could express recombinant exogenous genes encoding immunoglobulin heavy and light chain polypeptides in a given host cell. He notes that "the Rice paper does not address whether exogenous recombinant DNA sequences corresponding to heavy and light chain polypeptides could be independently expressed in a single host cell or whether those polypeptides could be assembled into immunoglobulin molecules or immunologically functional fragments." See, Harris Declaration, paragraph 32.

Dr. Rice also refutes the Examiner's suggestion that his PNAS paper demonstrated that expression of exogenous heavy and light immunoglobulin chain genes in host cells was "routine, resulting in assembly into immunoglobulins." First, as noted above, Dr. Rice explains that his paper does not disclose or suggest expressing exogenous heavy and light chain genes. Rice Declaration, paragraph 17. The 81A-2 cell line used in the paper was already expressing an endogenous heavy chain gene, and Rice does not even contemplate introducing a second, exogenous heavy chain gene in this cell line. Rice Declaration, paragraphs 12-13. Second, Dr. Rice points out that the his paper did not establish that the endogenous heavy chain and the exogenous light chain genes that were expressed produced "intact" immunoglobulins. As he explains in paragraph 16 of his declaration:

> Finally, my paper did not establish that the exogenous Ig light chain and the endogenous heavy chain polypeptides were properly assembled in the 81A-2 transformant into an Ig tetramer with antigen-binding activity. While the paper reports the presence of a higher molecular weight product that is approximately the size of an H_2L_2 tetramer, as shown in Figure 4 of the paper, we did not in any way prove these were antigen-binding H_2L_2 tetramers. On the contrary, we had no way to predict what the antigen binding specificity of such product would be, because, as discussed above, the antigen binding specificities of the component heavy and light chain polypeptides were different.

The Examiner confuses Rice's teaching of expression of an endogenous heavy chain gene and an exogenous light chain gene in a particular lymphoid cell line with the inventions

that are claimed in the '415 patent. The claimed inventions require expression of recombinant DNA sequences encoding exogenous heavy and exogenous light chain polypeptides. As Dr. Harris points out in his declaration at paragraph 36:

> In my view, the Rice paper does not address the question of whether exogenous light and heavy chain polypeptides, if expressed by a transformed host cell, will be assembled into an "intact" immunoglobulin molecule. Instead, what Rice shows is that it is possible to express an exogenous light chain polypeptide in a particular mature B-cell subclone that was already expressing an endogenous heavy chain and had lost its previous ability to produce endogenous light chain.

Thus, contrary to the Examiner's suggestions, the Rice paper does not even address the question of expressing exogenous heavy and light chain genes in a single host cell. The Examiner also mischaracterizes the actual observations in the Rice paper regarding the formation of immunoglobulins from the 81A-2 cell line.

Thus, Dr. Rice and Dr. Harris each specifically disagree with the Examiner's suggestion that, in early 1983, it "was known in the art that host cells could express 'heavy or light chains,' and that expression of both chains was routine, resulting in assembly into immunoglobulins." Instead, these experts, who are familiar with what the ordinary level of skill in the art was in early April of 1983 based on their own research activities in that timeframe, conclude precisely the opposite.

For these reasons, Rice would not have motivated a person of skill, in early 1983, to modify the process of claim 1 of the '567 patent by introducing exogenous DNA sequence encoding both the heavy and the light chain of an immunoglobulin. Notably, Rice itself does not suggest such a change. Similarly, Rice does not provide any guidance as to how a person would ensure that the heavy and light chain polypeptides encoded by the exogenous DNA, if expressed at all, would result in immunoglobulins. And, Rice certainly cannot be viewed as suggesting isolation of antigen-binding immunoglobulin molecules or fragments from the cell, given that Rice does not do so. Rice thus cannot support a conclusion by the Office that any of the independent claims of the '415 patent, based on the '567 patent claim, are defective for obviousness-type double patenting.

3. Claims 2, 3 and 25 Were Improperly Rejected and Are Not Obvious Based on Claim 1 of the '567 Patent Taken in View of Axel [See, OA, ¶ b, pages 8-9].

Claims 2 and 3 of the '415 patent are dependent on claim 1, and claim 25 is dependent on claim 21. As noted above, both claims 1 and 21 require expression of heavy and light immunoglobulin chains (or portions thereof) in a single host cell. Consequently, claims 2, 3, and 25 also contain this limitation. Claim 2 adds the requirement that the DNA sequences corresponding to the light and heavy immunoglobulin chains be on different vectors. Claim 3 adds the requirement that the DNA sequences be on the same vector. Claim 25 further limits claim 21 by requiring a vector to include DNA sequence encoding both a heavy and a light chain, as opposed to the portions of the heavy and light chain that make up a Fab region.

At page 9 of the Office Action, the Examiner cites Axel to support a rejection of claims 2, 3 and 25 of the '415 patent. The Examiner states that "Axel teaches transformed mammalian cells that produce multiple heterologous proteins on different vectors or on the same vector" and particularly cites to column 6, lines 44-66 and column 7, lines 3-9 of Axel.

As set forth above, the Examiner has not established a prima facie showing that claim 1 or 21 is anticipated by one or more claims that issued in the '567 patent. As such, a rejection of claims 2, 3 and 25, which depends on this initial finding, is improper.

Owners also disagree with the Examiner's suggestion that Axel would suggest, in any way, the idea of producing both heavy and light immunoglobulin chains in a single host cell. As explained above, a person of skill in the art would not read Axel to suggest expression of genes encoding two distinct proteins of interest (in addition to or in place of a marker gene) that are to be isolated from the same transformed host cell.

As such, the method defined by claim 1 of the '567 patent, taken in view of Axel, does not suggest processes yielding a host cell that independently produces both the heavy and light immunoglobulin chains and which yields an immunoglobulin molecule or an immunologically functional fragment comprising heavy and light chain elements. Because Axel does not describe or suggest such methods, the Examiner's suggestion that Axel renders obvious the incorporation of the DNA sequence encoding the heavy and the light immunoglobulin chains on a single vector, or on different vectors, reflects an improper reading of and reliance upon Axel.

For the foregoing reasons, Owners respectfully request the rejection of claims 2, 3 and 25 be withdrawn.

4. Claims 4 and 5 Were Improperly Rejected and Are Not Obvious Based on Claim 1 of the '567 Patent Taken in View of Axel and Kaplan. [See, OA, ¶ b, page 9]

Claim 4 requires that the vector recited in claim 1 be a plasmid, and claim 5 further limits claim 4 by requiring the vector to be the plasmid pBR322. Claims 4 and 5 are ultimately dependent on claim 1. As noted above, claim 1 requires expression of both the heavy and light immunoglobulin chains in a single host cell. Thus, claims 4 and 5 necessarily require that DNA sequence encoding both heavy and light immunoglobulin chains be incorporated into a single vector.

The Examiner cites Axel and Kaplan to teach, respectively, use of plasmids, and the specific plasmid pBR322 (Axel, col. 8, ll. 7-35; Kaplan, p. 10). The Examiner cites these references to suggest that they make obvious the use of a plasmid, and the pBR322 plasmid specifically, in connection with production in a single host cell that has been transformed with a single vector containing DNA sequence encoding both heavy and light immunoglobulin chains.

As set forth above, the Examiner has not established a prima facie showing that claim 1 defines a genus that is anticipated by a claim defining a species within that genus that issued in the '567 patent. As such, a rejection of claims 3, 4, and 5, is improper. Neither Axel nor Kaplan can cure the deficiencies of the primary basis of the rejection, namely, the lack of anticipation of the recited claims.

Moreover, for reasons set forth above, claim 1 of the '567 patent claims, taken in view of Axel, does not render claims 1, 2 or 3 of the '415 patent unpatentable for obviousness-type double patenting. Because Axel does not suggest producing both heavy and light immunoglobulin chains in a single host cell, Axel also cannot suggest use of a single plasmid, and specifically the pBR322 plasmid, to introduce DNA sequences encoding heavy and light immunoglobulin chains into a single host cell.

The Examiner cites Kaplan for the same reason that he cites Axel, namely, to support the view that plasmids were used to facilitate production of heavy and light immunoglobulin

chains in one host cell, and particularly that the pBR322 plasmid was a known plasmid useful for such purposes. Kaplan, like Axel, does not cure the defects of the primary basis of the rejection as set forth in the last Office Action.

The Examiner's characterization of Kaplan is plainly at odds with what the cited passage from the reference would mean to a person of skill in the art in early April of 1983. As Dr. Harris explains at paragraph 41 of his declaration:

> Kaplan, in my opinion, does nothing more than illustrate a general hypothetical approach that one might try to express an individual immunoglobulin light chain or heavy chain polypeptide. There are no examples provided in Kaplan of successful expression of immunoglobulin heavy or light chain polypeptides. Most significantly, nothing in Kaplan suggests that a heavy chain polypeptide and a light chain polypeptide should be produced in a single cell. Instead, as I read Kaplan, it suggests that a scientist could attempt to produce individual immunoglobulin chain polypeptides in separate host cell cultures. As such, I do not believe a scientist working in this field in early April of 1983 would have viewed Kaplan as suggesting the production of heavy and light immunoglobulin chain polypeptides in a single transformed host cell.

Thus, to a person of skill in 1983, Kaplan's brief and prophetic description makes clear only that the individual chains must be produced in individual host cells.

Kaplan thus does not suggest modifying the process of claim 1 of the '567 patent to transform a single bacterial host cell to produce both heavy and light immunoglobulin chains. It follows that Kaplan could not have suggested to a person of skill in the art that a plasmid, or the specific plasmid pBR322, could be used to insert a DNA sequence encoding heavy and light immunoglobulin chains into a host cell. Thus, claim 1 of the '567 patent, taken in view of Kaplan, would not have rendered claims 4 or 5 of the '415 patent unpatentable for reasons of obviousness-type double patenting. Owners respectfully request the rejection of claims 4 and 5 be withdrawn.

5. Claims 6-8, 19, and 26 Were Improperly Rejected and Are Not Obvious Based on Claims 1 and 21 of the '567 Patent Taken in View of Axel, Rice and/or Kaplan. [See, OA, ¶ b, pages 9]

Claims 6, 7, 8, and 26 ultimately depend from claims 1 and 21. The claims specify that the host cell being transformed according to independent claims 1 and 2 is a bacterium or yeast (claim 6), is either E. coli or S. cerevisiae (Claim 7), that the E. coli strain is X1776 (claim 8), or that the host cell is either E. coli or yeast (claim 26). Claim 19 depends from claim 1 and specifies that the host cell is a mammalian cell. As noted above, both claims 1 and 21 (and as a result, claims 6, 7, 8, 19, and 26) require expression of genes encoding the heavy chain as well as the light chain in a single host cell, and require assembly of an immunoglobulin molecule or an immunologically functional fragment comprising at least the variable portions of the heavy and light immunoglobulin chains.

The Examiner relies on Axel, Rice and Kaplan to reject claims 6, 7, 8, 19 and 26. In particular, the Examiner cites both Axel (column 5, lines 3-6 and lines 27-28) and Rice (page 7863) as rendering obvious the limitations found in the claims corresponding to use of mammalian cell lines, while page 10, lines 1-33 of Kaplan is cited for "teaching bacterial and yeast host cells."

As set forth above, the primary basis of the rejection of claims 6, 7, 8, 19, and 26 is that claims upon which these claims directly or indirectly depend (i.e., 1 and 21 of the '415 patent) define a genus that includes species defined by claim 1 of the '567 patent. For reasons provided above, this is an incorrect premise. As a result, the Examiner has not set forth a prima facie basis of obviousness-type double patenting of claims 6, 7, 8, 19, and 26.

In addition, Axel, Rice and Kaplan would not render obvious the cited claims. Claims 6-8 and 26 each require that the transformed host cell of the processes of claims 1 and 21 be either a bacterial or yeast cell, or more particularly, specific types of bacterial cells. The cited passages of Kaplan, however, provide no specific suggestion to use either E. coli cells, or the specific strain of E. coli specified in claim 8 (X1776) to produce, through recombinant means, an immunoglobulin. Claim 19, on the other hand, requires use of a mammalian cell for the host cell of claim 21. Again, the Examiner appears to be citing Axel and Rice for the proposition that such uses would have been obvious to a person of skill in the art. For the reasons set forth above, this reflects in inaccurate interpretation of the teachings of Axel and

Rice to a person of skill in early April of 1983. For the foregoing reasons, Owners respectfully request the rejection of claims 6-8, 19 and 26 be withdrawn.

6. Claims 9 and 29 Were Improperly Rejected and Are Not Obvious Based on Claim 1 the '567 Patent Taken in View of Axel and/or Rice. [See, OA, ¶ b, page 9-10]

Claim 9 of the '415 patent further limits claim 1, while claim 29 further limits claim 21. Claim 9 requires that the heavy and light immunoglobulin chains produced according to the process of claim 1 be produced in the host cell and be secreted therefrom as an immunologically functional immunoglobulin molecule or immunoglobulin fragment. Claim 29, on the other hand, further limits claim 21 by requiring that the heavy and light chains expressed by the host cell be secreted into the medium containing these host cells.

The Examiner has rejected claims 9 and 29 of the '415 patent on the following basis:

> Claims 9 and 29 of the '415 patent read on expression and secretion of an immunologically functional immunoglobulin. Axel teaches mammalian host cells for expressing proteins, expressly including antibodies. Axel, col. 5, lines 3-7 and 24-28. Rice demonstrates expression of a recombinant immunoglobulin light chain in a mammalian host cell. Rice, p.7863. Thus, '415 claims 9 and 29 are obvious variants of '567 claim 1 in view of Axel and/or Rice.

No other rationale is provided as to the basis for this rejection, and no independent observations are offered by the Examiner.

Neither Axel nor Rice supports a prima facie showing of unpatentability of claims 9 and 29 of the '415 patent. For reasons explained above, claims 1 and 21 of the '415 patent are not anticipated by claim 1 of the '567 patent, as these claims do not define a genus that includes the species defined by claim 1 of the '567 patent. The additional disclosures of Axel and Rice do nothing to remedy this underlying deficiency, and as such cannot support a prima facie rejection of claims 9 and 29 of the '415 patent when they are taken in view of claim 1 of the '567 patent.

Axel and Rice also do not suggest or render obvious claims 9 and 29 of the '415 patent. As explained above, Axel does not suggest processes where two distinct polypeptides

are produced and ultimately isolated from the transformed cell. Axel also does not describe processes where light and heavy chains of an immunoglobulin are produced, form an intact immunoglobulin molecule or immunologically active fragment, and are isolated from a single host cell. The Axel disclosure actually teaches away from the concept of expressing genes encoding heavy and light immunoglobulin chains in one host cell, as explained above.

Rice also does not render these claims obvious, because it does not suggest or describe production of exogenous heavy and exogenous light chains in one cell. Rice also plainly does not suggest production of immunologically functional immunoglobulins or fragments. Dr. Rice himself acknowledges that any IgG2 that could have been produced by his transfected lymphoid line would not exhibit selective binding of antigen due to the different antigenic specificities of the endogenous heavy chain and exogenous light chain studied, and because there was no evidence he actually produced a properly assembled immunoglobulin tetramer. See, Rice declaration, paragraphs 11 and 16.

For the foregoing reasons, Owners respectfully request the rejection of claims 9 and 29 be withdrawn.

7. Claims 10, 27, 28, and 31 Were Improperly Rejected and Are Not Obvious Based on Claims 1 and 21 of the '567 Patent Taken in View of Kaplan, Builder and the "admitted prior art." [See, OA, ¶ b, pages 10-11]

Claim 10 is dependent on claim 1, and claims 27, 28, and 31 are ultimately dependent on claim 21. Claim 10 further limits claim 1 by requiring the immunoglobulin light and heavy chains to be produced in insoluble form and be allowed to refold in solution to form an immunologically functional immunoglobulin molecule or fragment. Claims 27, 28, and 31 further limit claim 21 by requiring, respectively, that the heavy chain and the light chains or Fab region are deposited within cells as insoluble particles, where the chains are recovered from the particles by cell lysis followed by solubilization in denaturant, and wherein the heavy and light chain are recovered and reconstituted to form an immunoglobulin having specific affinity for a particular known antigen.

The Examiner cites Kaplan as teaching production of immunoglobulin polypeptides in bacterial or yeast systems. Kaplan and/or "the admitted prior art" also are cited by the Examiner as teaching steps for reconstitution of isolated immunoglobulin chains into

functional immunoglobulins (Kaplan, p. 10, lines 1-33;). Builder was relied upon for teaching that foreign proteins in bacteria or other host cells are frequently expressed as refractile bodies and further for teaching a procedure for recovering and refolding such refractile bodies (col. 2-6, schemes 1 and 2).

Each of the rejections of claims 10, 27, 28, and 31 is predicated on the incorrect determination by the Examiner that the independent claims upon which these claims ultimately depend are anticipated by the claims of the '567 patent. Without this predicate, there is no prima facie showing in the Office action that can support a rejection of these claims for obviousness-type double patenting.

Kaplan and Builder also cannot be portrayed in any way as describing or suggesting that a person of skill in the art modify the process of claim 1 of the '567 patent to result in the processes defined by claims 10, 27, 28 and 31 of the '415 patent. As noted above, Kaplan does not suggest production of heavy and light chains in a single transformed host cell. Builder is silent on the issue of production of immunoglobulin polypeptides, and cannot be cited to suggest that producing heavy and light chains in a single host cell would have been considered obvious. Thus, the Examiner has not set forth a prima facie showing of obviousness of claims 10, 27, 28 and 31 based on claim 1 of the '567 patent taken in view of Kaplan or Builder.

For the foregoing reasons, Owners respectfully request the rejection of claims 10, 27, 28, and 31 of the '415 patent to be withdrawn.

8. Claim 16 Was Improperly Rejected and Is Not Obvious Based on Claim 1 of the '567 Patent Taken in View of Axel or Kaplan. [See, OA, ¶ b, page 11]

Claim 16, which is dependent from claim 15, requires that the vector recited in claim 15 be a plasmid. As noted above, claim 15 requires a single vector that includes DNA sequences encoding at least the variable domain of an immunoglobulin heavy chain and a DNA sequence encoding at least the variable domain of an immunoglobulin light chain. Thus, claim 16 necessarily requires that both the first and second DNA sequences encoding the heavy and light immunoglobulin chains be incorporated into a single vector

The Examiner cites Axel and Kaplan to teach the use of, respectively, plasmids, and the specific plasmid pBR322 (Axel, col. 8, ll. 7-35; Kaplan, p. 10). The Examiner cites these references to suggest that they make obvious the use of a plasmid, and the pBR322 plasmid, specifically, as a vector having the first DNA sequence encoding at least the variable domain of an immunoglobulin heavy chain and the second DNA sequence encoding at least the variable domain of an immunoglobulin light chain located at different insertion sites.

As explained above, the Examiner has not established a prima facie showing that claim 15 defines a genus that is anticipated by a claim defining a species within that genus that issued in the '567 patent. As such, claim 5, taken in view of Axel or Kaplan does not establish a prima facie case of obviousness of claim 16 of the '415 patent.

Axel and Kaplan also cannot support a prima facie showing that claim 16 of the '415 patent would have been obvious based on claim 5 of the '567 patent. Claim 5 of the '567 patent is directed to a vector that would be suitable for use in the process defined by claim 1 of the '567 patent. That process requires only that a DNA sequence encoding either a heavy or a light immunoglobulin chain (but not both) be expressed, thus producing the heavy or light immunoglobulin chain. Standing alone, claim 5 of the '567 patent cannot be used by the examiner to motivate or enable production of heavy and light chains in a single host cell. And, as explained elsewhere, neither Axel nor Kaplan describe or suggest to a person of skill in the art, in early April 1983, adding a second DNA sequence encoding another immunoglobulin chain to the vector of claim 5. Thus, claim 5 of the '567 patent, taken in view of either Axel or Kaplan does not establish a prima facie showing of obviousness of claim 16 of the '415 patent.

For the foregoing reasons, Owners respectfully request the rejection of claim 16 of the '415 patent be withdrawn.

9. Claims 18 and 20 Were Improperly Rejected and Are Not Obvious Based on Claim 1 of the '567 Patent of Axel and Rice. [See, OA, ¶ b, page 11]

Claim 18 is directed to host cells that have been transformed to include at least two vectors, where at least one of the vectors incorporates a DNA sequence encoding at least the variable domain of an immunoglobulin heavy chain, and at least another vector incorporates a

DNA sequence encoding at least the variable domain of an immunoglobulin light chain. Claim 20 specifies that the host cell is a mammalian cell.

The Examiner cites claim 7 of the '567 patent in view of Axel or Rice to suggest that claim 18 is obvious. The Examiner further cites Kaplan to suggest claim 20 of the '415 patent is obvious, relying on Kaplan as teaching bacterial or yeast host cells for expressing recombinant heavy and light immunoglobulin chains.

For reasons analogous to those presented in respect of the rejection of vector claims above, the Examiner has not established a prima facie showing that claims 18 and 20 would have been considered obvious to a person of skill in the art in early April of 1983 based on claim 7 of the '567 patent taken in view of Axel or Rice, and taken further in view of Kaplan. Claim 7 of the '567 patent requires the presence of only a single vector containing a DNA sequence encoding a heavy or a light immunoglobulin chain. There is no requirement that an additional vector be present in the host cell, and the claim cannot be cited by the Examiner as providing any motivation to modify itself.

Finally, for reasons explained above, neither Axel, nor Rice, nor Kaplan cure the deficiencies of the rejection based on claim 7 of the '567 patent. Claim 7 of the '567 patent is directed to an embodiment of the inventions of the '567 patent that is useful for independent and distinct reasons (i.e., to produce a composition having a single chimeric immunoglobulin heavy or light chain). There is no inherent motivation to modify such a host cell to incorporate an additional vector containing a DNA sequence encoding another immunoglobulin chain. In addition, neither Axel, nor Rice, nor Kaplan suggestion production of the host cell defined by claims 18 and 20 of the '415 patent.

For the foregoing reasons, Owners respectfully request the rejection of claims 18 and 20 of the '415 patent be withdrawn.

10. Claim 22 Was Improperly Rejected and Is Not Obvious Based on Claim 1 of the '567 Patent Taken in View of Accolla (PNAS, 77:563-566, 1980) or the admitted prior art of Gold and Van Nagell. [See, OA, ¶ b, page 12]

Claim 22 further limits claim 21 by requiring that the heavy and light immunoglobulin chains are those of an anti-CEA antibody.

The Examiner cites the portion of claim 1 of the '567 patent specifying that the chimeric heavy or light immunoglobulin chain has specificity for a "particular known antigen." The Examiner then suggests that this portion of the claim, coupled with the fact that anti-CEA monoclonal antibodies were known prior to the filing date of the '415 patent, render claim 22 of the '415 patent obvious. In particular, the Examiner cites Accolla, Gold and Van Nagel as teaching anti-CEA monoclonal antibodies and suggests that Owners have admitted that anti-CEA antibodies are in the prior art.

The rationale articulated by the Examiner does not establish a prima facie showing of obviousness-type double patenting of claim 22. The Examiner appears to accept that neither claim 1 of the '567 patent nor the prior art teach production of heavy and light immunoglobulin chains that have specificity to the CEA antigen. As explained above, claim 1 of the '567 patent does not and cannot be cited by the Examiner as suggesting a modification of itself to require production of both heavy and light immunoglobulin chains of an anti-CEA antibody. And Accolla as well as the other publications mentioned, provide no motivation to alter the process of claim 1 of the '567 patent to arrive at claim 22 of the '415 patent. These publications are not in any way directed to production of heavy and light immunoglobulin chains in a single transformed cell. Instead, they discuss murine monoclonal antibodies produced by hybridomas. Thus, the fact that anti-CEA monoclonal antibodies were known in the art in early April of 1983 does not establish a prima facie showing that claim 22 of the '415 patent is obvious.

For the foregoing reasons, Owners respectfully request the rejection of claim 22 of the '415 patent be withdrawn.

11. Claims 23 and 24 Were Improperly Rejected and Are Not Obvious Based on Claim 1 of the '567 Patent of Taken in View of Rice. [See, OA, ¶b, page 12]

Claims 23 and 24 depend on claim 21. As noted above, claim 21 requires producing the heavy chain as well as the light chain (or portions thereof) in a single host cell. Consequently, claims 23 and 24 require production of both the heavy and light chain in a single host cell. Claim 23 further limits claim 21 by requiring that the heavy chain be of the gamma family, while claim 24 requires that the light chain be of the kappa family.

As explained above, the rationale underlying the rejection is the initial finding that claim 21 of the '415 patent is anticipated by claim 1 of the '567 patent. As explained above, that is an incorrect interpretation of claim 1 of the '567 patent, and does not establish a prima facie showing of anticipation or obviousness-type double patenting of claim 21 of the '415 patent.

The Examiner suggests claim 1 of the '567 patent when taken in view of Rice renders claims 23 and 24 obvious. Rice is not directed to methods of producing and isolating individual immunoglobulin chains, or immunoglobulin molecules or fragments. Rice provides no motivation to modify the process defined by claim 1 of the '567 patent to arrive at the process defined by claim 21 of the '415 patent. Rice also concerned an experiment in which a kappa light chain having an irrelevant (and unknown) antigen specificity was used to transform a lymphoid cell line that was producing an endogenous immunoglobulin heavy chain. As explained earlier, Rice does not suggest modifying the process of claim 1 of the '567 patent to arrive at the subject matter of claim 24 of the '415 patent. Moreover, there is no disclosure in Rice relating to transformation of any host cell to incorporate a DNA sequence encoding an immunoglobulin heavy chain of the gamma isotype. Thus, Rice provides no motivation or guidance to modify claim 1 of the '567 patent to arrive at what is claimed by claim 23 of the '415 patent.

For the foregoing reasons, Owners respectfully request the rejection of claims 23 and 24 of the '415 patent be withdrawn.

12. Claim 30 Was Improperly Rejected and Is Not Obvious Based on Claim 1 of the '567 Patent Taken in View of Kaplan. [See, OA ¶ b, pages 12-13]

Claim 30 is dependent on claim 21, and further requires that the host cell specified in claim 21 be a gram negative bacterium. It also requires that the heavy and light immunoglobulin chains be secreted into the periplasmic space of the host cell bacterium.

The Examiner bases the rejection on his incorrect view that claim 1 of the '567 patent "reads on" and thus encompasses not only processes where both heavy and light immunoglobulin chains are produced by a single host cell, but also processes where the host cell encompasses a gram negative bacterium. The Examiner also suggests that claim 1 of the '567 patent "reads on" processes where the heavy and light immunoglobulin chains are

secreted into the periplasmic space of a bacterium, presumably because the Examiner has found no limitation in claim 1 of the '567 patent excluding this possibility.

For reasons previously explained, the fact that claim 1 of the '567 patent "reads on" and thus dominates the subject matter defined by claim 30 of the '415 patent is irrelevant to the question of obviousness-type double patenting. Instead, the Examiner must compare what is required by the claims of the '415 patent to what is required by claim 1 of the '567 patent. Since there is no limitation in the '567 patent requiring (i) producing both heavy and light immunoglobulin chains in the same host cell, (ii) using a gram negative bacterium as the host cell, and (iii) secreting two chains into the periplasmic space of the bacterium, claim 1 plainly does not anticipate claim 30 of the '415 patent. Kaplan does nothing to remedy this deficiency because it neither suggests production of heavy and light chains in a single host cell, nor the idea that the host cell be a gram negative bacteria. It also does not suggest that immunoglobulin heavy and light chains can be secreted into and isolated from the periplasmic space of a bacterium. Thus, claim 1 of the '567 patent, taken in view of Kaplan, does not establish a prima facie showing of obviousness-type double patenting of claim 30 of the '415 patent.

For the foregoing reasons, Owners respectfully request the rejection of claim 30 of the '415 patent be withdrawn.

13. Claim 32 Was Improperly Rejected and Is Not Obvious Based on Claim 3 of the '567 Patent Taken in View of Kaplan and Builder [See, OA ¶ b, page 13]

Claim 32 of the '415 patent depends from claim 27 of the '415 patent, which, in turn depends from claim 21. Claim 32 claims the product produced by the process of claim 27; namely, an insoluble particle containing the heavy and light chains of an immunoglobulin.

The Examiner cites claim 3 of the '567 patent, which is directed to a composition comprising a chimeric heavy or light immunoglobulin chain. The Examiner also cites Kaplan as teaching bacterial and yeast host cells for producing recombinant immunoglobulin chains. The Examiner further cites Builder as demonstrating that "expression of exogenous or foreign proteins in bacterial or other host cells are frequently expressed as clumps of insoluble protein (i.e., refractile bodies). On this basis, the Examiner suggests that claim 32 of the '415 patent

is prima facie obvious in view of claim 3 of the '567 patent taken in view of Kaplan and Builder.

As explained above, claim 3 of the '567 patent does not anticipate claim 32 of the '415 patent. The distinctions between these claims are also not suggested by Kaplan or Builder. In this regard, as pointed out by Dr. Riggs, compositions containing only a chimeric heavy or light immunoglobulin chain have independent and distinct applications relative to compositions of insoluble particles containing heavy and light immunoglobulin chains. Thus, one possessing a composition containing only a chimeric heavy or light immunoglobulin chain would find no motivation, taken alone or in view of Kaplan or Builder, to add to that composition another immunoglobulin chain, particularly so as to yield an insoluble particle containing both chains. Claim 32 further requires that the process defined by claim 27 be employed to produce this insoluble particle, which is not suggested by Kaplan or Builder. Thus, the Examiner has failed to establish a prima facie showing that claim 32 of the '415 patent is obvious based on claim 32 of the '567 patent taken in view of Kaplan and Builder.

For the foregoing reasons, Owners respectfully request the rejection of claim 32 of the '415 patent be withdrawn.

14. Claims 34, 35, and 36 Were Improperly Rejected and Are Not Obvious Based on Unspecified Claims of the '567 Patent Taken in View of Axel, Rice, Kaplan, and Builder. [See, OA ¶ b, page 13-14]

Claims 34, 35 and 36, respectively, depend from claims 9, 10 and 33. Each of these claims further limits the process defined by claims 9, 10 and 33 by requiring an additional step of attaching the immunoglobulin molecule or fragment to a label or drug.

The rationale provided by the Examiner in respect of this rejection is that claims 9, 10 and 33 are obvious variants of the claims of the '567 patent. The Examiner then relies on Kaplan, Axel, Rice and Builder to suggest that claims 34 to 36 are obvious.

As explained above, claims 9, 10 and 33 are not anticipated by or obvious over any of the claims of the '567 patent. As such, the predicate of the Examiner's rationale for holding these claims to be obvious is incorrect. Accordingly, claims 9, 10 and 33 are not prima facie obvious based on claims of the '567 patent in view of Axel, Rice, Kaplan and Builder.

For the foregoing reasons, Owners respectfully request the rejection of claims 34 to 36 of the '415 patent be withdrawn.

VI. Conclusions

In view of the foregoing, the Applicants respectfully request that the rejections of the claims be withdrawn and that the Office issue a Reexamination certificate confirming claims 1 to 36 of the '415 patent. The Examiner is invited to contact the undersigned to discuss any issues not resolved by the above response.

The Commissioner is hereby authorized to charge Deposit Account No. 18-1260 for any additional fees required in connection with the filing of this Response.

Respectfully submitted,

Date: November 25, 2005

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that copies of this paper, the Declarations and Exhibits referred to herein are being served by first class mail delivery on the date shown below to Lisa V. Mueller, Wood, Phillips, Katz, Clark & Mortimer, 500 West Madison Street, Suite 3800, Chicago, IL 60661.

SIGNATURE

David L. Fitzgerald
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25 Nov 2005
DATE